VOLUME 12 NUMBER 4

ARCHIVES OF PATHOLOGY

OCTOBER, 1931

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00

Entered as Second-Class Matter, Jan. 20, 1926, at the Postoffice at Chicago, Illinois, Under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in the Act of Feb. 28, 1925, authorized Jan. 27, 1926.

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VOLUME 12 OCTOBER, 1931 NUMBER 4

PERIARTERITIS NODOSA COMPLICATED BY FATAL INTRAPERICARDIAL HEMORRHAGE

REPORT OF A CASE *

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Periarteritis nodosa or polyarteritis nodosa is a more or less generalized inflammation of the smaller arteries characterized at the beginning by acute degenerative and reactive changes in the vascular walls and later by the development of thrombosis, aneurysms and sclerosis. Clinically the symptomatology is protean, and a correct diagnosis during life is difficult. The prognosis is unfavorable; most of the patients die within a few months of the appearance of the symptoms. They either succumb to the toxemia resulting from extensive degenerative changes in the different organs and tissues or collapse suddenly from a fatal hemorrhage due to rupture of a small aneurysm.

Since the first comprehensive description of periarteritis nodosa by Kussmaul and Maier [1] in 1866, about 150 cases in man have been described in the literature. The ages of the patients varied from 3 months to 78 years, though the majority were in the third and fourth decades of life. Males were affected about four times as frequently as females (Arkin [2]). In addition, investigators have recorded cases of the condition in deer, cattle, swine and dogs (Nieberle [3]).

The etiology has been the subject of much speculation. Some writers (Ferrari,[4] Benda [5] and Meyer,[6] for example) have held that the underlying cause was weakness of the vascular walls induced by various toxic influences. Eppinger [7] referred all the lesions to congenital deficiency of the arterial media. Other writers (Graf,[8] Schmorl [9] and Verse [10])

* Submitted for publication, March 16, 1931.

* From the Pathological Laboratory and the First Medical and Surgical (Columbia) Divisions of Bellevue Hospital.

1. Kussmaul, A., and Maier, R.: Arch. f. klin. Med. **1**:484, 1866.
2. Arkin, A.: Am. J. Path. **6**:401, 1930.
3. Nieberle: Virchows Arch. f. path. Anat. **256**:131, 1925.
4. Ferrari, E.: Beitr. z. path. Anat. u. z. allg. Path. **34**:350, 1903.
5. Benda, C.: Berl. klin. Wchnschr. **45**:353, 1908.
6. Meyer, P.: Virchows Arch. f. path. Anat. **74**:277, 1878.
7. Eppinger, H.: Arch. f. klin. Chir. (supp.) **35**:42, 1887.
8. Graf, E.: Beitr. z. path. Anat. u. z. allg. Path. **19**:181, 1896.
9. Schmorl: Verhandl. d. deutsch. path. Gesellsch. **6**:203, 1904.
10. Verse, M.: Beitr. z. path. Anat. u. z. allg. Path. **40**:409, 1907.

considered the disease to be a form of syphilitic aortitis. Aschoff [11] suggested rheumatic infection as a possible causative factor. Many investigators (Klotz,[12] Lamb,[13] Jonas [14] and Ophüls [15]) have isolated different strains of pathogenic bacteria from cases of periarteritis nodosa, but such organisms have not filled adequately the rôle of an etiologic agent. All these theories have been found unsatisfactory and have been abandoned.

At present, opinion is sharply divided between the theory of von Hann,[16] who claimed that periarteritis nodosa is a disease entity caused by the action of a specific filtrable virus, and the theory of Spiro [17] and Gruber,[18] who claimed that the lesions are referable to the actions of many different noxious substances. Gruber is of the opinion that the arterial inflammation is a cellular reaction of the hyperergic type elicited by some toxin to which the tissues are sensitive. Unfortunately it is not possible to decide definitely at present on the correctness of these theories, as either one offers an equally good explanation of the pathologic changes encountered.

The results obtained by experimental inoculation of animals have been contradictory. Harris and Friedrichs [19] claimed that they had produced the disease in rabbits by inoculation with material from a case in man. Von Hann [16] asserted that he had in a similar fashion infected guinea-pigs. On the other hand, the experiments of Kopp,[20] Lemke,[21] Carling and Hicks,[22] Ophüls,[15] Sacki,[23] Otani [24] and Klotz [12] showed negative results. Evidently the final word on the etiology of this condition must be left to the future.

The arterial lesion in periarteritis nodosa may be characterized as primary necrosis of the wall followed by an attempt on the part of the body to repair the damage. The series of changes that occur may be described most effectively by dividing the process into four stages, as recommended by Arkin.[2] It must be kept in mind, however, that this

11. Aschoff: Verhandl. d. deutsch. path. Gesellsch. **10**:157, 1906.
12. Klotz, O.: J. M. Research **37**:1, 1917.
13. Lamb, A. R.: Arch. Int. Med. **14**:481, 1914.
14. Jonas: München. med. Wchnschr. **59**:1685, 1912.
15. Ophüls, W.: Arch. Int. Med. **32**:870, 1923.
16. von Hann, F.: Virchows Arch. f. path. Anat. **227**:1, 1919.
17. Spiro, P.: Virchows Arch. f. path. Anat. **227**:1, 1919.
18. Gruber, G. B.: Virchows Arch. f. path. Anat. **258**:441, 1925.
19. Harris, W. H., and Friedrichs, A. V.: J. Exper. Med. **36**:219, 1922.
20. Kopp, G.: Deutsche med. Wchnschr. **49**:1239, 1923.
21. Lemke, R.: Virchows Arch. f. path. Anat. **245**:322, 1923.
22. Carling, E. R., and Hicks, J. A. B.: Lancet **1**:1001, 1923.
23. Sacki, F.: Med. Klin. **20**:45, 1924.
24. Otani, S.: Frankfurt. Ztschr. f. Path. **30**:208, 1924.

division is more or less artificial, and that in a particular case the different stages may not be separated from each other in a clearcut fashion. The four stages are: (1) the primary or degenerative stage, (2) the acute inflammatory stage, (3) the granulation tissue stage and (4) the scar tissue or healed stage.

1. The primary stage is ushered in by acute coagulation necrosis of the media of the smaller arteries. The tissue immediately adjacent is filled with edematous fluid, and fibrin is deposited in the spaces. Polymorphonuclear leukocytes and a few eosinophils invade the affected area. The intimal endothelium becomes more permeable than in normal conditions. It may be crowded into the lumen of the blood vessel by the exudate in the subintimal space. In this early stage the adventitia is, as a rule, not involved.

There has been much discussion in the literature concerning which portion of the arterial wall is inflamed the earliest. As Gruber pointed out, however, the provocative agent reaches the vessel through the vasa vasorum, and the greatest reaction occurs in the layer of the wall that contains the most profuse supply of capillaries. In the larger vessels the outer layer of the media suffers the earliest, and in the smaller vessels the inner layer of the media is the first to be involved, because at these respective points the capillaries are the most abundant. In the arterioles, which lack vasa vasorum, the subendothelial layer shows the characteristic lesion, apparently because the causative agent attacks the vessel from the lumen. The location of the primary area of necrosis seems to depend on the size of the affected vessel.

The degree of arterial involvement is variable in different cases. In some instances only a portion of the circumference may be affected; in others a large annular segment may be inflamed. The number of arteries attacked also varies within wide limits. In case 1 described by Arkin,[2] there was a periarteritis nodosa throughout the body, while in the case reported by Fishberg [25] the arteries of the kidneys alone were affected. As a rule, however, most examples of the disease fall between these two extremes.

It has been estimated by Gruber (cited by Carr [26]) that the vessels are involved in the following relative frequency: the renal arteries, 80 per cent; the coronary arteries, 70 per cent; the hepatic arteries, 65 per cent; the arteries of the gastro-intestinal tract, 50 per cent; the pancreatic arteries, 25 per cent; the mesenteric arteries, 30 per cent; the arteries of the muscles, 30 per cent; those of the peripheral nerves, 20 per cent, and those of the brain, 8 per cent.

25. Fishberg, A. M.: Virchows Arch. f. path. Anat. **240**:483, 1923.
26. Carr, J. G.: M. Clin. North America **13**:1121, 1930.

2. In the acute inflammatory stage the media becomes completely necrotic, and the elastic tissue is destroyed. The vascular wall is infiltrated throughout by polymorphonuclear leukocytes, eosinophils, lymphocytes and plasma cells. The process may extend to the surrounding tissues so that an inflammatory perivascular zone forms around the vessel. The inflammation is acute, but never acquires frankly suppurative characteristics. The adjacent veins may be included in the exudate because of their proximity, but rarely show any lesions comparable with the process in the arteries. Walter [27] and Kountz,[28] however, described a mesophlebitis in their cases.

3. Sooner or later the polymorphonuclear leukocytes gradually disappear and are replaced by eosinophils, lymphocytes and plasma cells. At the same time granulation tissue wanders in from the adventitia, pervades the entire thickness of the vascular wall and even extends into the perivascular zone. The type of lesion at this stage indicates that the acute process has begun to subside and that repair is in progress.

During the progress of stages 2 and 3, the process in the arterial wall shows a tendency to develop in two different ways. In some vessels, the subendothelial connective tissue is incited to proliferate by necrosis of the media. This encroaches on the lumen of the vessel and narrows it eccentrically or concentrically; in a few instances the artery may be obliterated either by the intimal lesion or by the formation of secondary thrombi. In other arteries, the wall is weakened by the inflammation and small aneurysmal dilatations are formed along the course of the vessel. Thrombi occur in such conditions. Ruptures of the aneurysms are common, and blood may be extravasated into the surrounding tissues. Occasionally the hemorrhage may take place in one of the large cavities of the body and be fatal.

Generally the obliterating type of endarteritis and the small aneurysmal dilatations occur in the same case, though the latter tend to predominate. However, in some instances, aneurysms may be absent, and the arterial inflammation can be demonstrated only by microscopic examination (Wohlwill [29]).

At necropsy the aneurysms may be found in any part of the body, but are observed characteristically as nodules, measuring from 2 to 20 mm. in diameter, along the course of the coronary arteries, just under the pericardium, or as subperitoneal nodules along the insertions of the mesenteries to the various parts of the gastro-intestinal tract. They have been noticed in the peripheral nerves, in voluntary muscles, in the subcutaneous tissues and in the submucous layer of the stomach or of the intestines. In the solid viscera, as the liver and the kidneys, they

27. Walter, H.: Frankfurt. Ztschr. f. Path. **25**:306, 1921.
28. Kountz, W. B.: Arch. Path. **10**:55, 1930.
29. Wohlwill, F.: Virchows Arch. f. path. Anat. **246**:377, 1923.

are found in the connective tissue framework of the organ. Most of them are filled with thrombi of the bland type.

The usual result of the arterial changes, whether the process is the obliterating endarteritis or the aneurysmal dilatation, is to obstruct the vessel and hinder the supply of blood to the various viscera, so that areas of degeneration occur. As a consequence, multiple, bland, wedge-shaped infarcts occur in the liver and kidneys. Less often corresponding changes occur in the spleen, lung, heart, brain, gastro-intestinal tract, muscles, nerves, testicles and skin. In a few instances smaller areas of degeneration, not obviously connected with the obstruction of the arteries, are seen and are attributed by some investigators to the direct action of the toxic agent on the tissues.

The symptoms described in cases of periarteritis nodosa are referable to the toxic action of the causative agent and to the pathologic lesions in the arteries and viscera. In the first stage the disease may be latent or at most disclosed by a rise of temperature. During the second stage, when the arteries are inflamed, the signs of an acute infection make their appearance, such as continuous or intermittent fever, chills, polymorphonuclear leukocytosis and secondary anemia. Enlargement of the lymph nodes and of the spleen may occur.

When the second stage becomes well developed and the various organs are affected in different degrees, the symptoms become diverse. In some instances the predominant manifestations are those of renal insufficiency. In others the signs are those of circulatory failure. In still others there is great abdominal pain with severe attacks of jaundice, diarrhea, vomiting and the like. A fourth type is marked by the appearance of muscular pains and paralyses and, in general, all the stigmas of peripheral neuritis and myositis. Occasionally all of these different symptoms may be combined in the same patient.

The clinical picture as a rule is so variable that the diagnosis during life is often impossible. Some writers believe that different combinations of signs are suggestive of periarteritis nodosa. Meyer,[30] for example, favored the association of chlorotic marasmus, polyneuritis or polymyositis and severe gastro-intestinal symptoms as a characteristic syndrome. However, the disease can be identified during life only if some of the affected tissue is excised and subjected to microscopic examination. The diagnosis was made in the cases reported by von Hann,[16] Benedict,[31] Kopp [20] and Schmorl [9] through the removal of a subcutaneous nodule, and in the case reported by Manges and Baehr [32] by the excision of an abdominal nodule during the course of a laparotomy.

30. Meyer, P. S.: Berl. klin. Wchnschr. **58**:483, 1921.
31. Benedict: Ztschr. f. klin. Med. **64**:405, 1907.
32. Manges, M., and Baehr, G.: Am. J. M. Sc. **162**:162, 1921.

In general, the prognosis of periarteritis nodosa is unfavorable and most of the patients die at some point during the second and third stages. Gruber [18] places the average length of life at from seven to nine months. Some patients have lived longer; the patient whose case was reported by Wohlwill [29] lived twelve months, and the one whose case was reported by Spiro [17] lasted one and a half years. Fishberg's [25] patient had a clinical history of six days, but the disease must have had a much longer period of latency. The typical course is for the patient to have periods of acute illness lasting a few days or weeks, alternating with periods of quiescence. The inference is that during the stage of exacerbation the inflammation is spreading to other arteries. This is confirmed by the histologic examination of material recovered at necropsy. It is not uncommon to find some arteries showing acute necrotic inflammation and others showing well developed chronic endarteritis obliterans.

Death may result from the progressive cachexia which is referable to the inflammatory changes in the arteries and the degenerative changes in the viscera, or it may follow a sudden profuse hemorrhage from one of the smaller aneurysms in some part of the body. Such hemorrhages have been described as occurring in the brain (Dickson,[33] Arkin [2]), in the lung (Sternberg [34]), in the intestine (Lowenberg [35]), in the abdomen (Klotz,[12] Lemke [36]) and in the kidney (Schmidt,[37] Harris and Friedrichs,[19] Mertens,[38] Walter,[27] Fishberg [25]).

4. In some cases of periarteritis nodosa only a few arteries may be affected, and the process may not damage the important organs in a serious fashion. The acute inflammation then may subside, and the fourth stage or the stage of healing supervene. There is replacement of the injured vascular wall by scar tissue. This replacement occurs in three ways (Arkin [2]): One is by the continued proliferation of the subintimal connective tissue and the new formation of elastic fibrils. The second is by the organization and canalization of thrombi. The third is by the formation of scar tissue in and around the artery, forming typical nodular perivascular mantles. These processes tend to produce closure of the blood vessels, and degenerative changes and fibroses develop in the kidneys, liver, myocardium and other viscera. The patient who has reached this stage may live for years or until the reserve capacity of the damaged organs fails.

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33. Dickson, W. E. C.: J. Path. & Bact. **12**:31, 1908.
34. Sternberg, C.: Wien. klin. Wchnschr. **38**:729, 1925.
35. Lowenberg, W.: Med. Klin. **19**:207, 1923.
36. Lemke, R.: Virchows Arch. f. path. Anat. **240**:30, 1923.
37. Schmidt, J. E.: Beitr. z. path. Anat. u. z. allg. Path. **43**:455, 1908.
38. Mertens, E.: Klin. Wchnschr. **1**:1841, 1922.

REPORT OF CASE

The case of periarteritis nodosa reported here was that of a patient who died of an unusual complication.

A young Negro, aged 21, a plumber, was admitted to the First Medical Division of Bellevue Hospital, complaining of a severe pain in the midabdomen. He claimed that this pain started two weeks prior to admission, had been practically continuous since that time, and was most intense at night. It was so troublesome that he was afraid to eat for fear that the symptoms would increase. He had had one attack of vomiting about four or five days prior to admission.

On admission, physical examination disclosed a well developed and well nourished young man, rather somnolent in appearance, with throat and tonsils moderately inflamed. The abdomen was tender, especially on the right side. The temperature was 102 F. The rest of the examination disclosed nothing of importance. A tentative diagnosis of acute pharyngitis, acute gastro-enteritis and lead poisoning was made.

After four days' observation, the combination of symptoms led to the suspicion that there was an acute inflammatory process in the abdomen, such as cholecystitis or appendicitis. The patient was transferred to the wards of the First Surgical Division of Bellevue Hospital and an exploratory laparotomy was performed. At operation the peritoneal cavity was found to be normal. The abdominal wound was closed without further procedure and subsequently healed without complications.

The patient's symptoms, however, were not alleviated. The temperature continued high, and on the ninth day after the operation there was a recurrence of the abdominal pain. In addition, the leukocyte count revealed 27,400 cells, of which 90 per cent were polymorphonuclear leukocytes, 8 per cent lymphocytes, 1 per cent transitional cells and 1 per cent eosinophils. On the following day he had two convulsive seizures one hour apart. The tenderness on the right side of the abdomen was increased.

On the twenty-sixth day after operation, the patient was returned to the medical ward in about the same condition. Two days later, he suddenly died in the midst of a general tonic convulsion with a cry and biting of the tongue. The length of the clinical course since the onset of symptoms was forty-six days.

A blood culture taken on the sixteenth day after operation was negative. The Wassermann reaction of the blood was strongly positive (4 plus); that of the spinal fluid was negative. Examination of the urine two days before death showed only a sediment of pus and epithelial cells; fluoroscopic examination disclosed a slightly enlarged cardiac and aortic shadow. The other tests did not show anything unusual.

A positive diagnosis was not made, but it was believed that the patient was suffering from a generalized infectious process of unknown origin.

Necropsy.—Necropsy was performed four days after death. The body was that of a young Negro, 5 feet, 10 inches in height, weighing about 135 pounds (61.2 Kg.). The frame was slender; the muscular development was fair, and the nutrition was poor. There was a recently healed scar from an operation in the upper midline of the abdomen, about 5 inches (12.7 cm.) in length. No other abnormalities were noted externally.

On section, the abdomen showed some old, cobweb-like adhesions between the liver and the diaphragm and hyperplasia of the lymph nodes around the pancreas. The entire gastro-intestinal tract appeared normal on gross examination.

The liver was large, weighing 2,200 Gm. Multiple wedge-shaped anemic infarcts were scattered through the organ, especially under the capsule. They averaged from 4 cm. to 7 cm. in diameter and were yellowish. Some of the larger ones showed softening in the center, and the capsule immediately adjacent was thickened and covered with a rough, fibrinous deposit. The capsule of Glisson was increased in thickness. Some of the hepatic arteries were filled with grayish-red thrombi (fig. 1).

The spleen weighed 200 Gm. and was normal in size and appearance, except for the presence of small grayish-yellow infarcts, measuring from 3 to 6 mm. in diameter, scattered here and there just under the capsule.

The pancreas was normal, but the pancreatic artery showed small aneurysmal dilatations (from 6 to 10 mm. in diameter) that were filled with grayish-red thrombi.

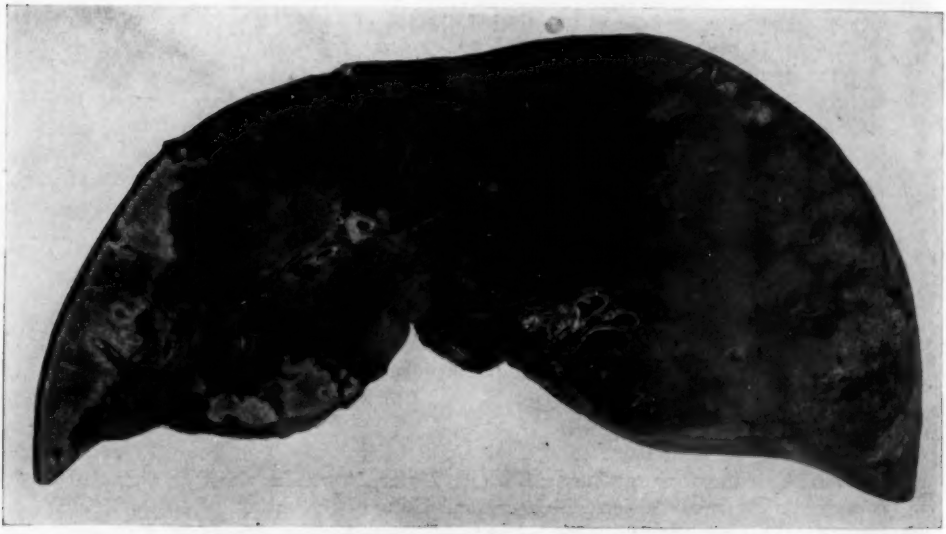

Fig. 1.—Segment of liver showing multiple infarcts.

The suprarenal glands were normal.

The kidneys together weighed 600 Gm. They were dull purplish brown, with a smooth outer surface. They were permeated with wedge-shaped anemic infarcts, from 3 cm. to 10 cm. in diameter, which were grayish yellow and situated just under the capsule. The vessels at the hilus of the kidneys were distended and filled with grayish-red thrombi.

The bladder, prostate, testes, aorta, cervical organs, brain and lungs were normal in appearance. The peripheral nerves and the skeletal muscles were not examined.

The bronchial lymph nodes were enlarged and matted together, and showed caseous tuberculosis. It is probable that these nodes played a part in increasing the size of the aortic shadow in the fluoroscopic examination.

The pericardial cavity was distended, and the heart was compressed by 300 Gm. of fluid blood and a blood clot. When the clot was removed, it was found to be attached to a bright red subepicardial nodule, 8 mm. in diameter, adjacent to the

descending branch of the left coronary artery, about 4 cm. distant from the aorta. This was found to be a small aneurysm of the coronary artery which had evidently ruptured, causing a fatal hemorrhage into the pericardial cavity. Unfortunately, the opening found in the nodule could not be identified with certainty as an antemortem rupture. Numerous other subepicardial aneurysms, from 5 to 20 mm. in diameter, were present, especially on the anterior surface of the heart, coming off from small branches of the coronary arteries, but not involving the main trunks. Section of the aneurysms disclosed the presence of grayish-red thrombi. They

Fig. 2.—Heart showing aneurysms of smaller branches of coronary arteries.

gave the heart a lumpy appearance. The heart itself weighed 340 Gm. and was markedly contracted. It did not show anything else unusual (fig. 2).

Diagnosis.—The diagnosis made at necropsy was: periarteritis nodosa involving the arteries of the heart, liver, kidneys, spleen and pancreas; rupture of a small branch of the left coronary artery; hemorrhage into the pericardial cavity with compression of the heart; multiple infarcts of the liver, kidneys and spleen, and tuberculosis of the bronchial lymph nodes.

Histologic Observations.—The various tissues were fixed in formaldehyde and embedded in celloidin, and sections were stained in hematoxylin and eosin, as a routine. A few sections were stained with van Gieson's stain combined with

Weigert's elastic tissue stain. A few were stained with Levaditi silver stain for spirochetes, but these organisms could not be found.

The infarcts in the liver and kidney were demonstrated, on section, to be the usual type of anemic infarct.

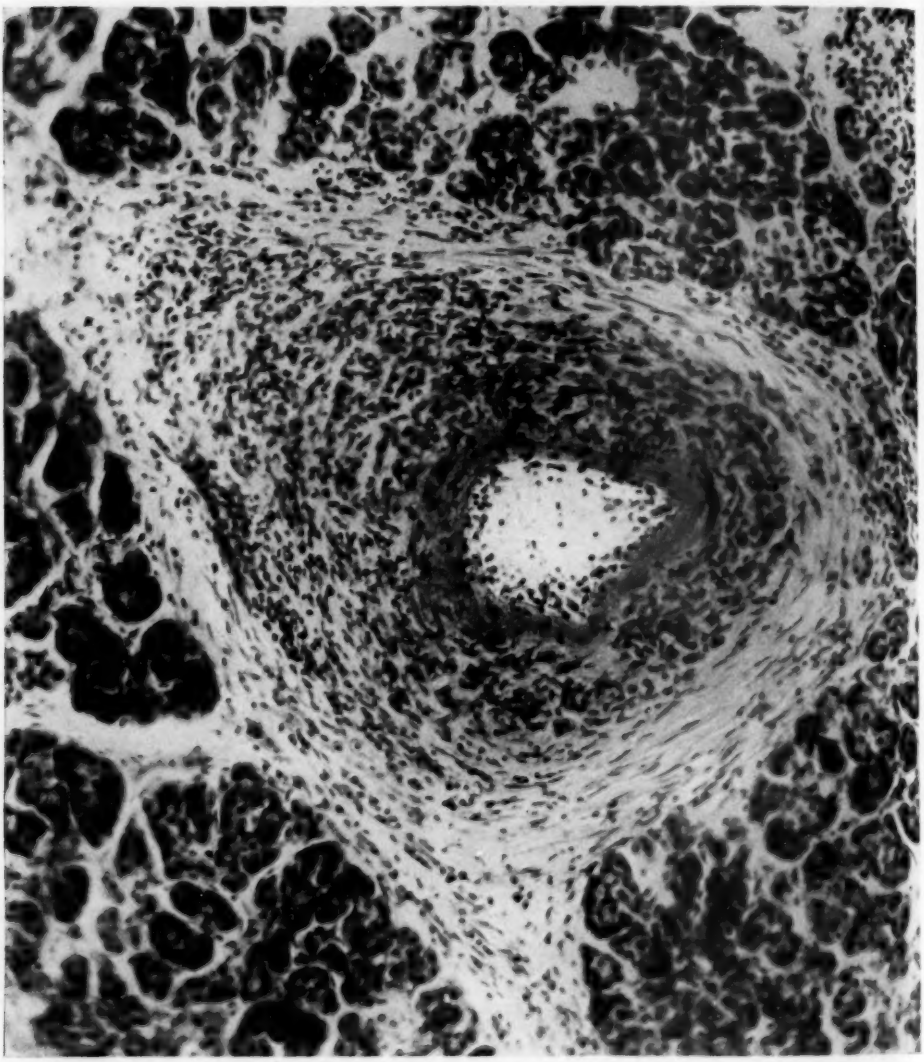

Fig. 3.—Small artery of pancreas in stage of acute inflammation: media necrotic and all layers infiltrated with leukocytes and other cells.

The caseous areas in the bronchial lymph nodes were found to represent a chronic tuberculous process. Sections through the lymph nodes around the pancreas showed merely lymphoid hyperplasia, probably the result of irritation.

The heart, liver, kidneys, pancreas, stomach, duodenum, mediastinum and epididymis were the seat of arterial inflammation. In other tissues, such as the aorta, lungs, central nervous system, skin and lymph nodes, lesions of this type were not found.

The histologic picture presented by the inflamed arteries was typically that of periarteritis nodosa. Early lesions characteristic of stage 2 were found in the stomach and duodenum and could be demonstrated only on microscopic section. The affected arteries were located in the subperitoneal layer and the outer muscular layer, while the arteries in the mesentery and submucous layer were normal. The media of the inflamed vessel was swollen, fibrillar, necrotic and markedly eosinophil. It was infiltrated with polymorphonuclear leukocytes and with a smaller portion of eosinophils, lymphocytes and plasma cells. The adventitia showed the same type of exudate and, in addition, numerous large ovoid cells were present; this layer was widened to several times the normal thickness. The subintimal layer was infiltrated with polymorphonuclear leukocytes, and the endothelium was pushed into the lumen by the process. The elastic tissue in the artery was destroyed. Some of the arteries of the mediastinum, epididymis and pancreatic tissues showed the same process (fig. 3).

In addition, an endarteritis obliterans suggesting the latter part of stage 3 was present in many small arteries of the epididymis, pancreas, heart, liver and kidneys. The lumen of the artery was narrowed and in some cases practically occluded by the proliferation of the fibrous tissue of the intima. The musculature was intact, and the elastic fibers were fairly well developed as a rule. The adventitia was normal, except in a few instances where there was a considerable deposit of brownish, granular, intracellular pigment.

The aneurysms in the heart, liver and kidneys were large vessels containing bland, laminated thrombi. The cells of the muscular layer were fairly well preserved, but areas of necrosis were found in the media here and there. The media and the adventitia were both extensively infiltrated with granulation tissue, polymorphonuclear leukocytes and other inflammatory cells.

The veins in the different sections were not inflamed.

In the heart and kidneys small collections of leukocytes were found without any apparent connection with the lesions in the blood vessels. In the tissues of the posterior mediastinum, many areas of infiltration by plasma cells were noted. It is possible that these lesions were caused by the toxemia.

The spleen and one of the pericardial aneurysms were cultivated for bacteria, but the results were negative.

SUMMARY

An example of periarteritis nodosa in a young colored man, 21 years of age, is depicted. The chief symptoms were severe abdominal pain, polymorphonuclear leukocytosis and a temperature of 102 F. A laparotomy was performed under the impression that the patient was suffering from an acute abdominal condition, but the peritoneal cavity was found to be normal. Subsequently the patient's condition did not improve, and forty-six days after the onset of symptoms he died in the midst of a generalized convulsion.

Necropsy disclosed multiple aneurysms of the coronary arteries and a hemorrhage into the pericardial cavity from the rupture of one of them. Aneurysms also were found in the arteries of the pancreas, liver,

kidneys and spleen. An acute necrotic arteritis and a chronic obliterating arteritis without the formation of aneurysms were noted in the pancreas, mediastinum, epididymis and gastro-intestinal tract. Multiple infarcts were present in the liver, kidneys and spleen. The pathologic changes were typical of periarteritis nodosa and were sufficient to account for the clinical symptoms of the patient.

The length of the clinical course was forty-six days—an apparently rapid course—but there is reason for believing that the arterial inflammation began long before the symptoms started. In some places the patient showed an acute necrotic arteritis of recent origin and in other areas an endarteritis obliterans of much longer duration. Evidently the different vessels were affected at different intervals.

EFFECTS OF ULTRAVIOLET RAYS, RADIUM AND X-RAYS ON PROTEINS*

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The increasing use of ultraviolet rays, radium and x-rays as therapeutic agents has awakened the interest of the scientific world in the changes that these same agents produce in the substances of the organism. This is especially true with respect to what is probably the most important constituent of protoplasm, protein.

The changes occurring in irradiated solutions of proteins may be considered from both the physicochemical and the purely chemical points of view. Of these, the physicochemical point of view has proved especially satisfactory and fruitful when applied to colloids in general and to proteins in particular, as in the well known investigations of Hardy, Robertson and Pauli. The following studies on the effects of irradiation with rays of short wavelength on various types of protein solutions were made, therefore, with the aid chiefly of physicochemical methods.

1. The effects of irradiation on a solution of protein depend on whether or not the particular protein is soluble in water and whether the solution contains an electrolyte or is electrolyte-free. Neglect of these factors probably accounts for the discordant results recorded in the literature. Only water-soluble proteins can, of course, be studied in an electrolyte-free condition. Irradiation of electrolyte-free solutions of serum albumin or of pseudoglobulin results in a denaturation and coagulation of the protein, as was first shown by Hardy [1] for radium, by Dreyer and Hanssen [2] for ultraviolet rays and by myself [3] for x-rays. In 1 per cent solution of albumin, the first sign of flocculation appears after ten minutes' irradiation at a distance of 30 inches

* Submitted for publication, March 9, 1931.

* From the Department of Colloid Chemistry, Temple University Medical School, D. T. McCarthy Foundation, Philadelphia.

* The experimental work referred to in this paper was partly carried out in the Institutes for Physiology and Medical Colloid Chemistry of the University of Vienna, Austria.

* The author is indebted to Dr. Arthur G. Cole, of the University of Illinois, College of Medicine, for aid in the preparation of the English version of this paper.

1. Hardy, W. B.: J. Physiol. **29**:29, 1903.

2. Dreyer, G., and Hanssen, O.: Compt. rend. Soc. de biol. **145**:234, 1907.

3. Spiegel-Adolf, M.: Unpublished observations.

(76.2 cm.) from the mercury arc,[4] after nine hours' irradiation with 80 mg. of metallic radium [5] or after exposure to at least 72 Holzknecht units of x-rays.[8] These data were obtained with sterile solutions of protein, since Spiegel-Adolf and Pollaczek [6] showed that bacterial infection affects the time required and may even entirely prevent the flocculation of the protein. If, however, irradiation is continued on sterile solutions, precipitation of the protein results. It is necessary to point out, in connection with these experiments, that the electrolyte-free solutions of protein need not be at their iso-electric points in order to achieve these results.

2. There is little information available concerning the nature of the chemical changes that proteins undergo during denaturation. The investigations of Harris [7] indicated that denaturation is accompanied by oxidation. The amount of oxygen bound by the protein must, however, be small, since coagulation by ultraviolet rays is observed in an atmosphere of nitrogen that contains only small amounts of oxygen.[8] Experiments made by Spiegel-Adolf and Fernau [9] indicated that the nitrogen content of proteins is not changed by coagulation with radium. These results suggest the possibility that denaturation of proteins by various types of rays involves a physicochemical rather than a chemical change in the protein.

3. In order to analyze the character of the denaturation produced by irradiation, it was compared with another type of denaturation that has been more extensively studied. In 1925, I [10] showed that the denaturation of serum albumin by heat was, when carried out under certain specified conditions, reversible. Wells and Lewis [11] previously had reached a similar conclusion from their experiments on the sensitization of guinea-pigs to heat-coagulated protein. Besides this, some authors, as Emden,[12] believe that the irreversibility of certain colloidal changes bears a direct relationship to biologic age and death. It is therefore of considerable interest to compare proteins denatured by irradiation and by heat and to determine whether the changes in the protein produced by irradiation are reversible or not. Experiments

4. Spiegel-Adolf, M.: Strahlentherapie **89**:367, 1928.
5. Fernau, A., and Spiegel-Adolf, M.: Biochem. Ztschr. **204**:14, 1929.
6. Spiegel-Adolf, M., and Pollaczek, K. F.: Biochem. Ztschr. **214**:175, 1929.
7. Harris, D. T.: Biochem. J. **20**:271, 280 and 288, 1926.
8. Spiegel-Adolf, M.: Biochem. Ztschr. **197**:197, 1928.
9. Spiegel-Adolf, M., and Fernau, A.: Unpublished observations.
10. Spiegel-Adolf, M.: Biochem. Ztschr. **170**:126, 1926.
11. Wells, H. G., and Lewis, J. H.: J. Biol. Chem. **59**:3, 1924.
12. Emden: Klin. Wchnschr. **8**:1913, 1929.

carried out for this purpose showed that there was an important difference between denaturation caused by heat and that due to irradiation. The latter proved to be an irreversible reaction when examined by the methods employed in the study of the denaturation due to heat. The results obtained were the same regardless of whether ultraviolet rays or radium had been used for the precipitation of the protein. In either case the precipitates formed exhibited properties that were distinctly different from those of albumin precipitated by heat.

4. If, instead of electrolyte-free solutions of proteins, solutions are used that contain small amounts of acid or of alkali, different effects are obtained by irradiation. In all of these experiments, the amount of irradiation is sufficient to cause complete precipitation in an electrolyte-free solution of protein of the same concentration. Such solutions are completely denatured by irradiation even in the presence of electrolytes. In these cases, however, precipitation occurs only when the concentration of acid or alkali in the solution is too small to dissolve the denatured protein. (I was able to show that the acid-binding capacity of serum albumin was not affected by denaturation with the mercury arc. This means that the hydrogen ion concentrations of such solutions do not change under treatment with rays of short wavelength.) The same solutions exhibit a similar behavior when heated. Although irradiation may produce no visible change in solutions that contain sufficient acid or alkali, the fact that a change has taken place may be demonstrated in various ways. Removal of the acid or of the alkali by dialysis or electrodialysis results in a flocculation of both the heated and the irradiated protein. Although small differences in color and even in odor may be detected, it is difficult to demonstrate by chemicals methods that the protein has suffered any change. That such changes have taken place may, however, be indicated by optical methods.

5. Solutions of protein exhibit absorption bands in the ultraviolet region of the spectrum. The addition of small amounts of acid or alkali, sufficient to prevent coagulation of the protein during irradiation, does not affect these absorption spectrums. When, however, such solutions are exposed to the mercury arc or to the rays of radium, a marked increase in the absorption of light of short wavelength may be observed [13] (figs. 1 and 2). These changes may be confirmed and demonstrated in a different way. For this purpose, Hausmann and Spiegel-Adolf [14] made use of a small ring of glass fixed to a quartz

13. Spiegel-Adolf, M., and Krumpel, O.: Biochem. Ztschr. **28**:190, 1928.

14. Hausmann, W., and Spiegel-Adolf, M.: Klin. Wchnschr. **6**:2182, 1927.

plate and divided by a small piece of glass into two separate compartments. One of these compartments was filled with a solution of irradiated protein, while the other contained a nonirradiated control. The entire apparatus was then placed on the forearm of a man and exposed to the mercury arc for fifteen minutes. After this period, and for some hours afterward, the section of skin covered with the nonirradiated

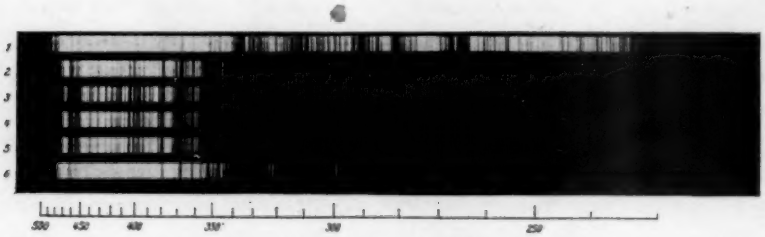

Fig. 1.—Influence of ultraviolet rays on the absorption spectrums of solutions of protein (the concentration of protein is the same in all solutions): (1) iron spark; (2) control acidified solution of serum albumin; (3) control alkaline solution of serum albumin; (4) irradiated acidified solution of serum albumin; (5) irradiated alkaline solution of serum albumin, and (6) nonirradiated, electrolyte-free solution of serum albumin.

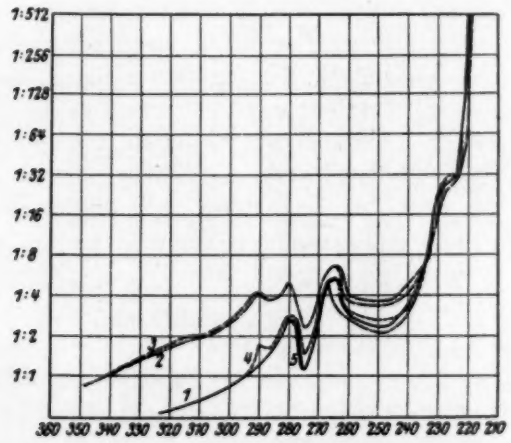

Fig. 2.—Absorption curves of solutions of protein: (1) pure serum albumin; (2) irradiated acidified solution of serum albumin; (3) irradiated alkaline solution of serum albumin; (4) control solution of alkaline serum albumin, and (5) control solution of acidified serum albumin. The ratios at the left represent the concentrations of protein; the numerals at the bottom, the wavelengths in millimeters.

protein showed a distinct erythema (fig. 3). That part of the skin covered by the irradiated protein showed either no change or only a very slight change, thus proving that irradiated proteins are less per-

meable to light of short wavelength than nonirradiated ones. These experiments have been repeated, with similar results, by various investigators. It has even been suggested that the increased absorption of light by irradiated proteins may have some bearing on those cases in which, after repeated exposure to the mercury arc, the skin becomes insensitive to further exposure without any pigmentation having occurred. The same experiment was repeated, with use of cultures of bacteria and agar containing red blood corpuscles instead of the skin, with similar results. Together with Oshima,[15] I was able to show by means of this method that the growth of various kinds of bacteria was arrested by rays of different wavelengths.

It was shown by Lewis [16] that the various serum proteins absorb different amounts of ultraviolet rays. The globulins exhibit the great-

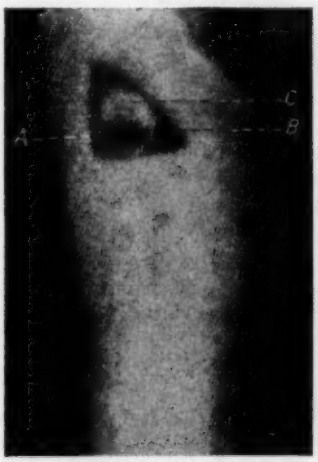

Fig. 3.—Effect of irradiation on the permeability of a solution of protein to ultraviolet rays: *A*, portion of skin covered by quartz alone; *B*, portion of skin beneath control solution of protein, and *C*, portion of skin beneath irradiated solution of protein.

est absorption, while the albumins show the least. Pseudoglobulin exhibits an absorption intermediate between the other two. When these proteins are irradiated, however, these differences in absorption disappear almost completely, for the albumins exhibit the largest increase in absorption, while the globulins show the least.[8] This does not mean that irradiation transforms albumins into globulins, as occasionally indicated in the literature. It means merely that the albumins,

15. Spiegel-Adolf, M., and Oshima, Z.: Biochem. Ztschr. **208**:32, 1929.

16. Lewis, S. J.: Proc. Roy. Soc., London **93**:178, 1921-1922.

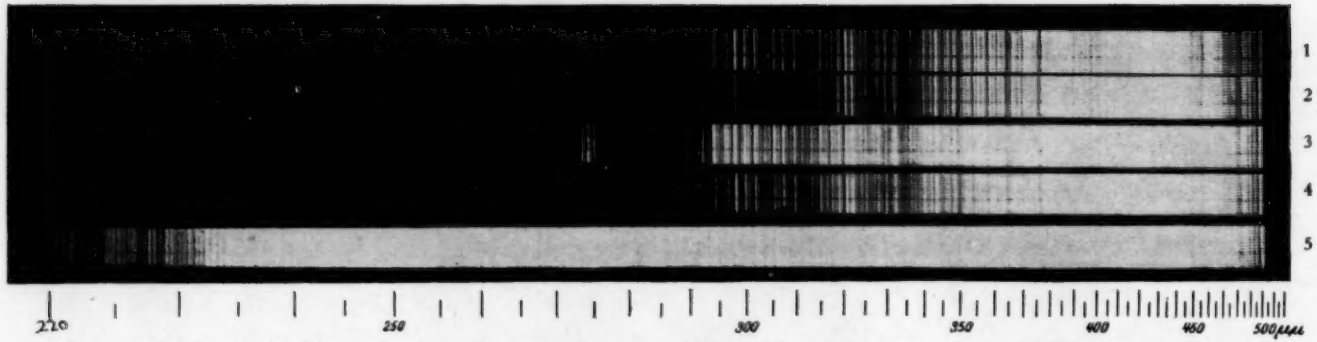

Fig. 4.—Influence of radium on absorption spectrums of solutions of protein: (1) control solution of alkaline serum albumin; (2) solution of alkaline serum albumin irradiated by radium; (3) solution of alkaline serum albumin diluted with water (dilution of 1:1); (4) solution of alkaline serum albumin of same concentration as solution 3 irradiated by radium, and (5) empty cell.

when irradiated, acquire some of the physicochemical properties of the globulins. They lose, either completely or in part, their solubility in water, and the colloidal character of their solutions changes from a hydrophilic to a hydrophobic one. They may be salted out of solution by smaller concentrations of salt in much the same way that the primarily hydrophobic globulins usually are. Proteins exposed to the rays of radium behave in exactly the same way; i. e., they become more opaque to light of short wavelength [17] (fig. 4). It may seem at first glance, that radium exerts a lesser effect on proteins than does the

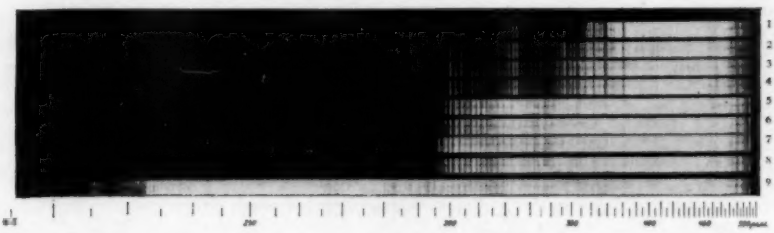

Fig. 5.—Influence of heat on absorption spectrums of concentrated solutions of proteins: (1) alkaline solution of serum albumin, boiled; (2) alkaline solution of serum albumin, unheated; (3) acid solution of serum albumin, boiled; (4) acid solution of serum albumin, unheated; (5) alkaline solution of egg albumin, boiled; (6) alkaline solution of egg albumin, unheated; (7) acid solution of egg albumin, boiled; (8) acid solution of egg albumin, unheated, and (9) empty cell.

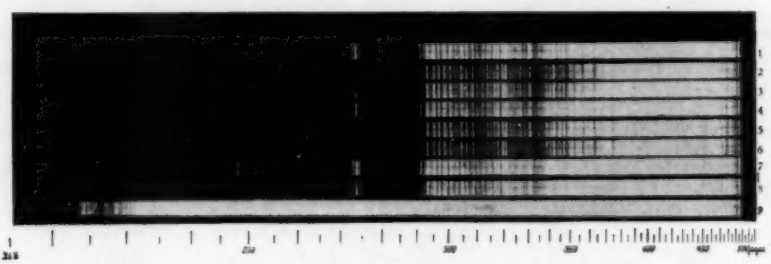

Fig. 6.—Influence of heat on absorption spectrums of dilute solutions of protein: (1) alkaline solution of serum albumin, unheated; (2) alkaline solution of serum albumin, boiled for fifteen minutes; (3) alkaline solution of serum albumin, boiled for one hour; (4) acid solution of serum albumin, unheated; (5) acid solution of serum albumin, boiled for fifteen minutes; (6) acid solution of serum albumin, boiled for one hour, and (9) empty cell.

mercury arc. The exposure used in the case of radium was, however, not long enough to permit its effects to be compared quantitatively with those produced by ultraviolet rays.

17. Spiegel-Adolf, M., and Krumpel, O.: Biochem. Ztschr. **190**:28, 1929.

It was indicated that the denaturation of electrolyte-free solutions of protein produced by heating differed from that caused by irradiation in that the former process was reversible. This criterion for differentiating between the two types of denaturation cannot be applied to proteins denatured in the presence of alkali, because, under these conditions, the heated protein also undergoes an irreversible change. Differences between alkaline solutions of protein denatured by heat and those denatured by irradiation may, however, be detected easily with the aid of the quartz spectrograph. It is observed (fig. 5) that with the same concentration of protein, there is no increase in absorption produced by heating the solution. With higher dilutions of protein, slight changes in absorption may be detected (fig. 6). These changes are not, however, at the same wavelength as before, and in some of the solutions there is no increase in absorption, but rather the reverse. Some of the solutions become even more permeable to light of short wavelength when heated.[17] Solutions of heated protein cannot, therefore, be used to filter ultraviolet rays, as in the experiments with irradiated protein. In all of the experiments mentioned, the solutions of protein were heated for fifteen minutes at the temperature of boiling water. Increasing the time of heating to one hour had no effect on the results obtained.

6. Since the results obtained by spectrographic examination are of considerable importance in the study of the constitution of chemical substances, it was considered worth while to seek other methods to check the results described. For this purpose I made use of another optical method. The optical rotation of the substance under examination is measured with light of several different wavelengths, and the results obtained are plotted on a diagram in which the abscissa represents the square of the wavelength, and the ordinate the reciprocal of the specific rotation. For simple substances, it is found that the plotted values lie on a straight line that intersects the abscissa at a point that represents the wavelength of the chief absorption band of that particular substance. This method, used by Lowry and Dickson, is based on the equations of Drude. It was applied to solutions of proteins subjected to ultraviolet rays, radium and heat.[18] It was found that the points of intersection of the various curves with the abscissa were not affected by the addition of sufficient alkali to prevent coagulation of the protein. This result is in accordance with the conclusions drawn from the spectrographic investigations. It was found, also, that heating the solution of protein had no effect on the inter-

18. Spiegel-Adolf, M.: Biochem. Ztschr. **213**:475, 1929.

section of its curve with the abscissa (fig. 7). The quotient between the specific rotations at certain specified wavelengths, known as the dispersion quotient,[19] remains at the value characteristic for the unheated solutions. Irradiated protein, on the other hand, exhibits an entirely different behavior. Although the curve of optical dispersion is still a straight line, it intersects the abscissa at a point that indicates a longer wavelength for the characteristic absorption band. These results are in direct agreement with those obtained by spectrographic examination. The dispersion quotient reaches a value usually observed in ketones derived from amino-acids by oxidation. In the first experiments, the protein was denatured by ultraviolet rays. Further experiments on the effects of radium on the same protein led to practically the same results.

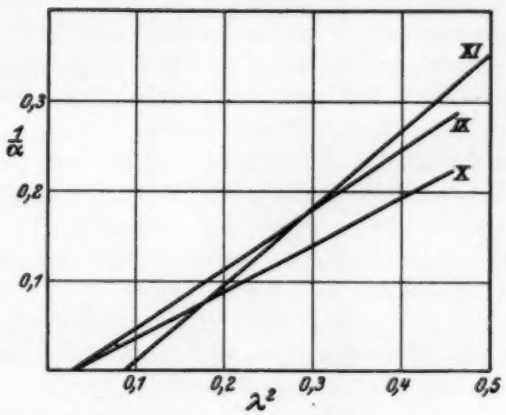

Fig. 7.—Optical dispersion of heated and irradiated alkaline solution of pseudoglobulin: *IX*, control alkaline solution of pseudoglobulin; *X*, alkaline solution of pseudoglobulin, heated, and *XI*, alkaline solution of pseudoglobulin, irradiated.

7. Experiments were also carried out on the immunologic properties of the heated and irradiated proteins.[20] In the presence of sufficient acid to prevent coagulation of the protein, it was possible to show that solutions that had been heated gave precipitates with serums against the unheated protein, whereas solutions irradiated with the mercury arc failed to give any reactions. When heated proteins were used for immunization, the antiserums obtained also reacted with unheated protein. When irradiated proteins were used for immunization, however, three out of four serums obtained failed to react with the untreated protein.

19. The dispersion quotient is $\frac{[a]_F}{[a]_C}$

20. Spiegel-Adolf, M., and Higuchi, S.: Unpublished observations.

8. The results of the investigations lead to two principal conclusions: First, as shown by means of the various independent methods, rays of short wavelengths produce effects on proteins that differ from those observed when the protein solutions are heated to 100 C. Second, various types of rays, such as ultraviolet rays, x-rays and radium, produce effects that are qualitatively, though not quantitatively, similar. These conclusions are applicable only to proteins. It was pointed out that coagulation of the protein results from a few minutes of irradiation with the mercury arc and that three hours' exposure to x-rays (72 Holzknecht units) and nine hours' exposure to 80 mg. of radium are required to produce the same results. This suggests that only a small part of the energy of the x-rays and of radium is active in the coagulation of the protein, whereas most of the ultraviolet rays are absorbed by the protein. This may be due to the fact that the principal absorption bands of the solutions of proteins lie in this region of the spectrum. If, therefore, it were possible to convert part of the energy of radium and of x-ray radiations into ultraviolet rays, a possibility which is in accordance with Stokes' law, the effects of these radiations on proteins should be intensified. For this purpose, I made use of the property of certain crystals to fluoresce in the ultraviolet region when irradiated by radium or x-rays. Salts of tungstic acid were not used because I wished to avoid the production of light of longer wavelength.[21] The crystals used were enclosed in quartz tubes to avoid contact with the liquid. By means of this method, I was able to show that whereas proteins irradiated by x-rays and radium without ultraviolet fluorescence exhibit no changes, the same proteins similarly treated in the presence of the fluorescent material are coagulated.[22] Similar experiments were also carried out with red blood corpuscles and with such living cells as Paramecium. The first changes in red blood corpuscles produced by irradiation with x-rays appear in one-fourth the time when a quartz tube containing the fluorescent crystals is immersed in the suspension. Paramecia, which cannot be killed by radium, or which may be destroyed only with great difficulty, promptly died when irradiated under these conditions. In the case of the red blood corpuscles, almost the same effects are produced when filtered x-rays are used, indicating that ultraviolet rays may be called forth in such places, as tissues, where it can not penetrate from the outside. Further investigations are necessary to determine whether this method is of any therapeutic value. I am at present studying its application to tumor tissues in mice. The well known results of ultraviolet rays in tuberculosis suggest an attempt in this direction.

21. Perrine, J. O.: Physiol. Rev. **22**:48, 1923.
22. Spiegel-Adolf, M.: Klin Wchnschr. **9**:1615, 1930.

PSEUDOHERMAPHRODITISMUS MASCULINUS EXTERNUS ASSOCIATED WITH SUPRARENAL HYPERPLASIA AND VASCULAR HYPERTENSION

REPORT OF A CASE *

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Fairly well defined clinical syndromes are known to exist in association with malformations of the suprarenal gland, and since experimentally it is impossible to reproduce many of these, it becomes increasingly important to record those instances in which clinical findings may be correlated with postmortem observations in order that recognition of the syndromes may be expedited and insight into essential relationships deepened. The case submitted here is of exceptional clinical, as well as pathologic, interest. The patient, a person 26 years old, to all outward appearances a female, had not undergone the changes associated with puberty and had had for a known period of six years a high blood pressure, which led to her sudden death from spontaneous intracerebral hemorrhage. Postmortem examination disclosed a remarkable degree of hyperplasia of suprarenal tissue associated with pseudohermaphroditismus masculinus externus, marked cardiovascular changes and apparent absence of the pineal gland.

REPORT OF CASE

Clinical History.[1]—The patient, a school teacher in the twenties, was a young person of unusual mental attainments, an excellent scholar, who was studying for the degree of Doctor of Philosophy in history. She was very nervous and excessively vivacious in her speech, but was not irritable. Although 6 feet tall (183.5 cm.), she was handsome, essentially feminine, not only in appearance, but also in her reactions to, and her relations with, her external environment. She was admitted to Barnes Hospital on April 23, 1923, during a fairly typical attack of appendicitis, several of which she had had before. No operation was performed. She gave a history of having had recurrent attacks of heart trouble with "dropsy" since her childhood. She stated that she menstruated once when she was 15 years old, but had not done so since. The menses, she stated, were scanty and lasted one day. Subsequently she never had any monthly pain or cramplike sensations. She occasionally had nosebleed in childhood. Physical examination

* Submitted for publication, May 11, 1931.
* Read before the Chicago Pathological Society, April 13, 1931.
* From the Department of Pathology of the University of Chicago and the Illinois Central Hospital.

1. The Barnes Hospital in St. Louis gave us access to the clinical record.

revealed a tall, fairly well nourished white woman who was very restless and fidgity. The skin was rather dry, and there was a marked absence of axillary and pubic hair. The breasts were very small and infantile. A soft systolic murmur, best heard at the apex of the heart, was not transmitted to the axilla. The apical impulse was in the fourth interspace 9 cm. from the midsternal line. The eyegrounds were normal. The blood pressure varied from 180 systolic and 140 diastolic to 150 systolic and 98 diastolic. So much muscular resistance was encountered that accurate palpation of the pelvic organs was impossible. It was thought best not to disturb the patient further at the time, but to make pelvic examination under anesthesia should the need become urgent. A lateral stereoscopic x-ray picture of the skull suggested an oxycephalic syndrome and increased intracranial pressure. There were albumin and hyaline and granular casts in the urine. There was some renal insufficiency. The blood chemistry was normal. The patient was discharged on May 4, 1923. On June 10, 1923, she reentered Barnes Hospital prior to a tonsillectomy which had been advised on her previous admission. The blood pressure varied from 195 systolic and 145 diastolic to 175 systolic and 120 diastolic. On the second day following the operation an attack of gastric tetany developed. The blood pressure dropped to 100 systolic and 60 diastolic, and uremic symptoms appeared. The nonprotein nitrogen rose to 111 mg., and the urine contained albumin and many hyaline and granular casts. The renal function showed marked impairment. Subsequently the uremic symptoms cleared, and the blood pressure rose. At the time of the patient's discharge, on June 25, 1923, the blood pressure had risen to 155 systolic and 105 diastolic. During the following summer the patient had occasional severe headaches. The hands and eyelids were swollen at times, especially in the mornings and evenings. She tired easily. On Sept. 10, 1923, she reentered Barnes Hospital for a reexamination. The renal function was improved, and the level of nonprotein nitrogen was lower. Following a series of tests the blood pressure rose to 210 systolic and 180 diastolic, and the patient had a severe headache with nausea and vomiting. An electrocardiographic tracing showed no abnormalities. During the remainder of the patient's stay in the hospital the blood pressure stayed constantly around 190 systolic and 158 diastolic. The urine showed a trace of albumin and a few white blood cells and granular casts. The nervousness and excitability were apparently increased. The patient was discharged on Sept. 17, 1923. Later she refused treatment with ovarian extract for infantilism. Friends stated that she had severe headaches at frequent intervals. The clinical diagnosis at this time was chronic diffuse nephritis, hypertension, oxycephaly, hypogonadism and infantilism. In 1928, the patient was acting as dean and teacher of history in a girl's school and was under some strain about her work. Death came suddenly while she was in consultation with the head of her school. She slid down from her chair unconscious, but breathing, and died within a few minutes.

Necropsy.—Necropsy was performed at the Illinois Central Hospital in Chicago. The examination disclosed a well developed, well nourished white woman, looking about 26 years of age, weighing 140 pounds (63.42 Kg.) and having a height of 6 feet, 1 inch (185.42 cm.). There was a slight amount of hair on the face, a few hairs on the labia, but no pubic hair. The external genitalia resembled those of a preadolescent girl. The breasts were poorly developed. On the right side a testicle, 2.5 cm. long and 1.1 cm. wide, with a rudimentary epididymis, lay in a sheath in the abdomen retrocecally (fig. 1). On the same side a vas deferens, 11 cm. long, apparently entered the wall of the bladder just posterior to the urethral attachment. At this point there was a small mass of solid tissue,

resembling muscle, measuring 2 by 2 by 0.6 cm., which was loosely attached to the wall of the bladder. No uterus or ovaries were present. The vagina was 3 cm. long and 1 cm. wide and ended blindly (fig. 2). There was a slight nodular thickening at the apex of the vagina which might correspond to the cervix uteri. A rudimentary round ligament was present.

The suprarenal glands were greatly increased in size and together weighed 46.5 Gm. The left suprarenal gland was in the normal position. It was 7 cm. long, 4 cm. wide, and from 0.5 to 1 cm. thick. The right was 8 cm. long, 4.5 cm. wide and 1 cm. thick. At the lower pole of the right suprarenal gland there was a nodule that was dark reddish brown flecked with yellow. It measured 2 cm. in length and 1 cm. in width.

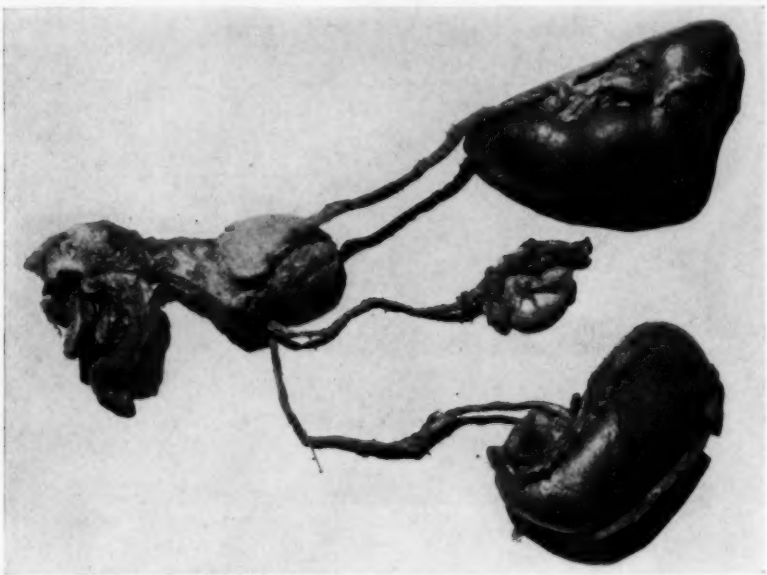

Fig. 1.—The preadolescent testicle and epididymis which lay behind the cecum. From it the vas deferens passes to end blindly in a mass of undifferentiated muscle tissue lying behind the bladder in the usual site of the prostate. Note the very small size of the bladder.

There was a marked hyperplasia of the intestinal lymphoid follicles and mesenteric lymph nodes. The spleen weighed 380 Gm., and the germinal follicles were unusually prominent.

The left kidney was about the normal size and was edematous. The cortex was slightly narrowed, and the markings were indistinct. The capsule stripped easily, leaving a smooth surface. The pelvis seemed normal. The right kidney was somewhat smaller, but similar to the left. The bladder was extremely small. It measured 4 cm. in its greatest external diameter, and the wall was 1 cm. thick, so that the cavity was extremely small. The urethral wall was greatly thickened.

The liver weighed 2,420 Gm. and was a hand's breadth below the costal margin. It was dark reddish brown. No other significant changes were noted in the abdominal cavity.

The heart weighed 430 Gm. The apex of the heart was made up entirely of the left ventricle. The left ventricular wall measured from 16 to 22 mm., and the right from 2 to 5 mm., in thickness. There were no valvular lesions, except for tiny warty vegetations on the corpora arantii of the aortic cusps and on the mitral leaflets, which were otherwise smooth and shining. There were small atheromatous patches in the coronary arteries, which were unobstructed. Small atheromatous patches were present on the arch of the aorta, and yellow and white atheromatous patches at the opening of the abdominal vessels. The aorta in its thoracic and abdominal portions was normal in size.

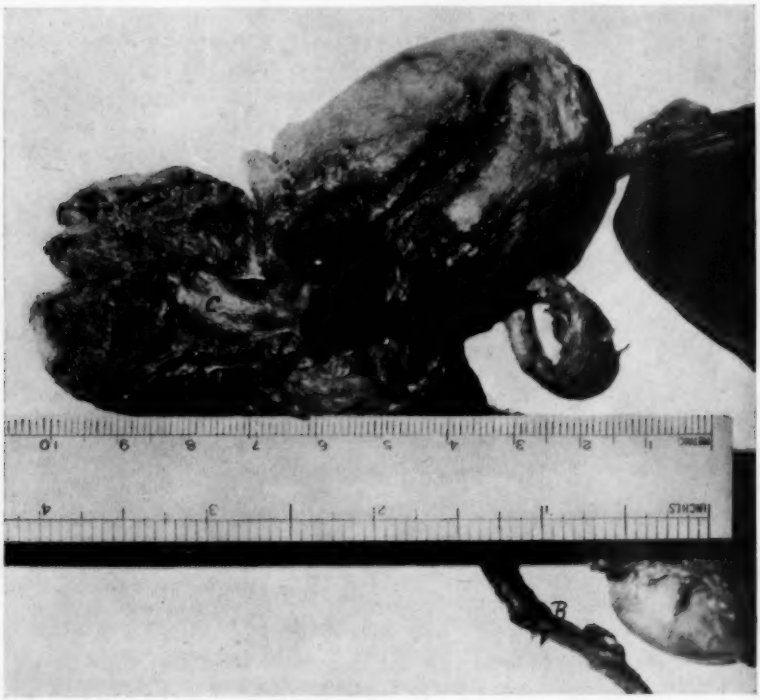

Fig. 2.—Bladder and vagina. The greatly thickened wall of the bladder with its small cavity is seen above (*A*). Behind and below is the vas deferens (*B*), ending blindly in a mass of muscle tissue behind the bladder at the site of the prostate. The rudimentary vagina lies open (*C*).

There were marked bilateral pulmonary hyperemia and edema. The thyroid gland weighed 27.5 Gm. and contained glistening colloid. The thymus gland was not mentioned. There were no other significant changes in the thorax. A generalized arteriosclerosis was present.

There was no evidence of external trauma to the skull. The brain was edematous; the convolutions were flattened and the sulci narrowed. There were hemorrhages in the leptomeninges over the pons and extending down into the spinal canal. An extensive hemorrhage led on the right to a total interruption of the connection of the cortex with the internal capsule. Of the basal ganglions on the right, only a small medial part containing the anterior part of the internal

capsule was present. The left basal ganglions showed flattening of the nucleus caudatus and an outward convex curve of the internal capsule. The basilar and vertebral arteries displayed an astounding degree of arteriosclerosis. The hypophysis appeared grossly normal. The pineal gland was not definitely recognizable.

The microscopic examination of the tissues revealed conditions as follows:

Suprarenal Glands: In sections stained with hematoxylin and eosin, the fibrous capsule of the suprarenal gland was not thickened. The zone glomerulosa was narrow and in places was entirely absent. In many regions the characteristic arrangement of this zone in spherical or oval groups of epithelial cells was lost, the epithelium being definitely compressed between the capsule and the hyperplastic cells of the deeper cortical layers. Where not compressed, the epithelial cells of the zona glomerulosa were columnar. Their cytoplasm stained lightly with eosin and was somewhat granular, and the nuclei were rich in chromatin. In an occasional region, cells from the zone glomerulosa appeared to invade the capsular tissue immediately adjacent to the gland. The characteristic arrangement of the zona fasciculata and the zona reticularis in long columns and irregular anastomosing cords was, for the most part, lost, although an occasional suggestion of fascicular arrangement was present in the zona fasciculata. The epithelium consisted of large, irregularly arranged, polyhedral cells with an acidophilic cytoplasm and spheroidal, vesicular nuclei which varied somewhat in size and were less rich in chromatin than were those in the zona glomerulosa. Many of these cells had a distinctly foamy cytoplasm, and many others toward the inner layers of the cortex were heavily pigmented with a brownish granular pigment. There was an enormous diffuse hyperplasia of the epithelium of these two layers, which could not be distinguished one from the other. In an occasional region, there was a tendency toward encapsulation of small nodular groups of cortical epithelium by fibrous tissue. The cortical cells were seen to invade the glomerular zone, in regions crowding it aside and becoming adjacent to the capsule, at times invading this structure, and occasionally forming small extracapsular adenomatous nodules the substance of which was continuous with that of the gland. In regions this extra-capsular tissue was not limited by a capsule of its own, but infiltrated the adipose tissue (fig. 3). The medulla was likewise invaded by cortical epithelium, and in places islands of cortical tissue were present in the medulla. There was no apparent increase in connective tissue stroma or in vascularity. Regions of the suprarenal gland were distinctly vacuolated, being composed of signet ring cells resembling those of adipose tissue. There were occasional foci of lymphoid cells, the largest one of which contained many cells with large eosinophilic granules and an occasional mononuclear giant cell. Outside the capsule there were many circumscribed nodules of cortical tissue. In places these cells were seen to invade the adipose tissue, not being limited by a capsule.

There was an extensive diffuse increase in medullary tissue, the cells of which were polyhedral or irregularly oval, and were arranged with marked irregularity. The nuclei were spherical or slightly ovoid, were somewhat vesicular, and contained a moderate amount of chromatin. The cytoplasm was somewhat basophilic and slightly granular. A few of the cells possessed foamy cytoplasm and others contained brownish granular pigment. In regions there was a slight infiltration by the signet ring cells. The medullary tissue had a bizarre arrangement. In places the medulla was very narrow; in others it became irregularly widened. Some regions appeared as islands and streaks of cells completely surrounded by cortical tissue. In others the cortical cells were diffusely infiltrating the medullary tissue. The medullary stroma seemed normal in amount, and there was no increase in vascularity. In sections stained with van Gieson's connective tissue

stain, there appeared an increase in connective tissue in the occasional regions where there was an attempt at nodular arrangement and encapsulation of the cortical epithelium. In one region in the medulla, the stroma formed relatively heavy connective tissue strands. Aside from that in the region mentioned the connective tissue was not increased.

Testis: In sections stained with hematoxylin and eosin, the testis was surrounded by a delicate fibrous tunica albuginea, which projected into the gland at one point, forming the mediastinum or hilus testis. The tubules appeared to have a definite fibrous tissue basement membrane, were small, and except for an occasional suggestion of a lumen were closely packed with epithelial cells resembling

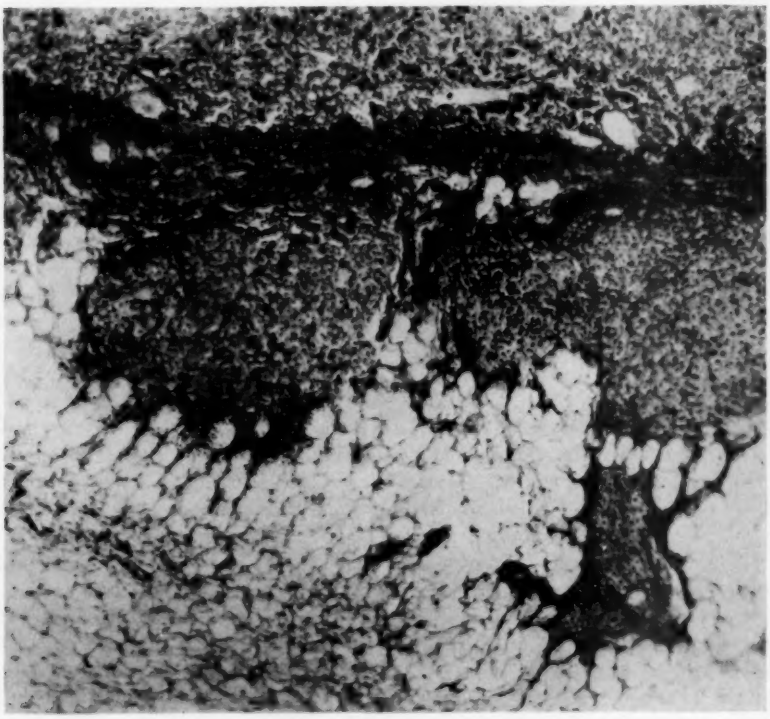

Fig. 3.—Suprarenal gland showing invasion of the adjacent adipose tissue by outgrowth of cells of the suprarenal cortex, infiltrating like neoplastic tissue, although the cells seem to be normal cortical cells; × 75.

Sertoli cells of an embryonic testicle (fig. 4). Toward the capsule the tubules were most numerous, but were widely separated and irregularly scattered throughout the substance of the gland, which was made up almost entirely of large polygonal cells, the cell outlines of which were often indistinct (fig. 5). The nuclei were round or slightly oval and were pale and vesicular. The cytoplasm was more acidophilic than that of the tubular epithelium and was often finely vacuolated. The cells exhibited no pigmentation and resembled Leydig cells. In one region in a subcapsular position there was a small, circumscribed nodule apparently composed of closely packed tubules filled with a mass of cells having round or oval, hyperchromatic nuclei (fig. 4). The cell outlines could not be

distinguished. The van Gieson stain showed a fairly heavy connective tissue stroma in the nodule. Throughout the substance of the gland the van Gieson stain demonstrated a stroma that was not appreciably increased in amount. Near the hilus of the gland there was a region where large vacuoles resembling fat cells were present in the substance of the gland. The epididymis was small and of infantile type, and occasionally a duct showed papillary epithelial proliferation. Mallory's stain showed only a delicate collagenous reticulum around the blood vessels and tubules. The epididymis was widely separated from the capsule of the testis by loose areolar connective tissue.

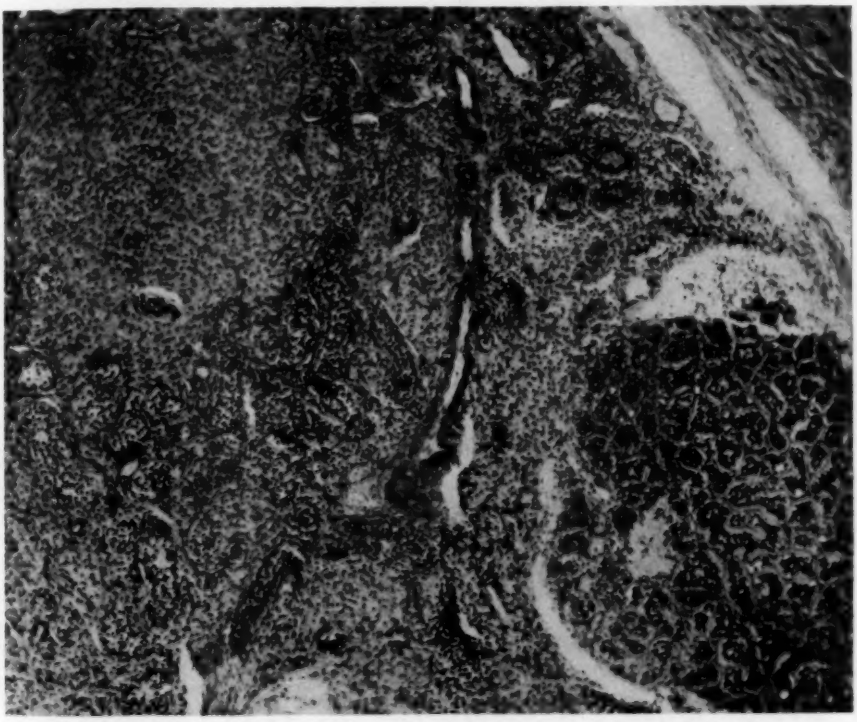

Fig. 4.—Testicle. The photomicrograph shows the general structure, with but few, undeveloped seminiferous tubules, a diffuse cellular intertubular growth and a nodule of undeveloped tubular structures; × 75.

Other Organs: The nodule at the base of the bladder consisted of a mass of spindle cells in poorly defined bundles resembling underdeveloped nonstriated muscle fibers. No glandular elements were seen, and there was nothing to indicate whether this was a rudimentary prostate or uterus. The vagina showed no histologic changes.

The anterior lobe of the hypophysis showed a slight increase in connective tissue. The epithelial cords were often irregular in arrangement, sometimes apparently hypertrophied and containing more colloid than normal.

Serial sections through a small mass of tissue occupying the site of the pineal gland failed to reveal any trace of pineal tissue.

In the region of the cerebral hemorrhage, only the usual infiltration by blood was seen, there being no other changes recognizable in a preparation stained with hematoxylin and eosin, except an occasional blood vessel surrounded by cells filled with brown pigment as if from a previous small hemorrhage.

The thyroid gland showed no definite abnormalities.

Peyer's patches of the ileum exhibited tremendous hyperplasia, each follicle being greatly enlarged with a conspicuous germinal center. There was also a

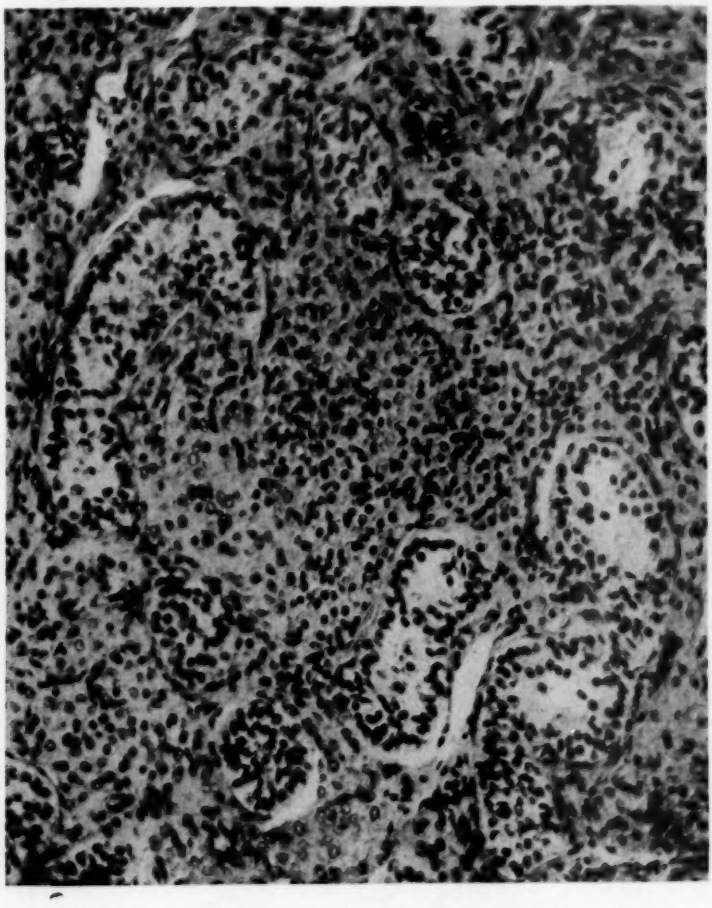

Fig. 5.—Testicle; × 200. The photomicrograph shows the undeveloped state of the organ, which much resembles the testicle of an embryo in an early stage. The tubules are lined with cells resembling Sertoli cells. Between the tubules are sheets of cells resembling Leydig's cells as seen in undeveloped testicles.

diffuse lymphoid infiltration between the follicles. Otherwise the intestine was normal. The mesenteric lymph nodes showed marked lymphoid hyperplasia, giving rise to a picture that was distinctly "mulberry" in type. The spleen showed marked increase in the size of the malpighian bodies which had fetal characteristics.

The myocardium was somewhat hypertrophied, but otherwise showed no changes. The aorta showed thickening of the intima with but slight atheroma. The media was not changed. The arteries everywhere showed thickening of the intima without degenerative changes.

The kidneys showed occasional small areas of localized atrophy and fibrosis beneath the capsule, which did not usually extend deeply into the cortex. Between these areas the renal tissue was approximately normal. No evidence of old or recent inflammatory changes was found in the glomeruli outside of these arterio-

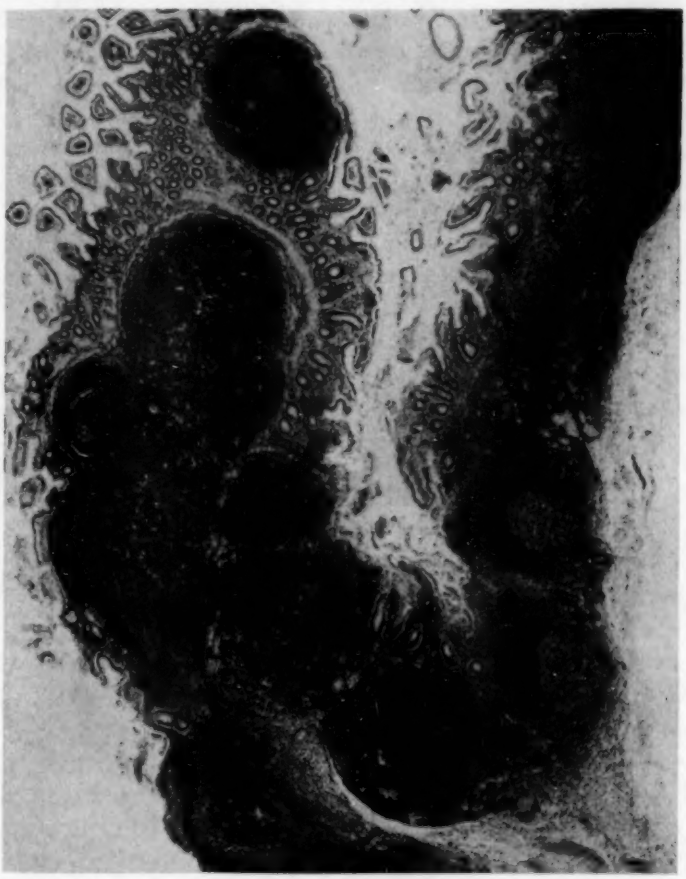

Fig. 6.—Ileum showing the great hyperplasia of the lymphoid tissue; × 33.

sclerotic scars. A few collecting tubules contained calcified masses, apparently calcified epithelium. The arterial walls were greatly thickened, the small arterioles being often almost occluded and their walls hyalinized. These observations indicate that such renal changes as were present were the result of arteriosclerosis. There was no evidence of a primary glomerulonephritis.

The urinary bladder was extremely small and showed an enormous hypertrophy of the muscular coats, but otherwise appeared normal. The urethra was normal.

The liver and the pancreas showed no significant changes.

COMMENT

Classification of Pseudohermaphroditism According to Klebs.—Neugebauer,[2] in his extensive monograph on pseudohermaphroditism, uses the generally accepted classification of Klebs, recognizing pseudohermaphroditism of two types, the masculine in which the gonads are testicles, and the feminine in which they are ovaries. Both groups are further subdivided into the internal, external and complete types. External pseudohermaphroditism occurs when only the external genitalia, internal when only the internal organs, and complete when both internal and external organs, are not properly developed. The case reported here is obviously one of pseudohermaphroditismus masculinus externus; that is, the gonad was the testicle and the external genitalia were feminine. This group is rarely found associated with hyperplasias and neoplasms of the suprarenal cortex, by far the larger percentage of such associations belonging to the feminine pseudohermaphroditic and suprarenal virilism group. It is significant that statistically approximately 15 per cent of all pseudohermaphrodites are estimated to have bilateral hyperplasia of the suprarenal cortex.

Classification of Suprarenal Pseudohermaphroditism According to Gallais.—Largely through the correlation of clinical and postmortem observations it has become recognized that malformations of the suprarenal cortex have some definite relationship to anomalies of sexual development. Credit is given to Bullock and Sequeira [3] for emphasizing this relationship, and although references to the probable relationship are to be found in the older literature, it is since their paper that a considerable literature has grown up about the subject. The clinical picture brought about in the presence of hyperplasia or tumor of the suprarenal cortex when related to sexual anomalies has been given by Gallais [4] the name "le syndrome génito-surrénal," and he has divided cases in which this syndrome appears into four groups based on the age of the person at the time of the appearance of the symptoms.

Group I, "le pseudohermaphroditisme surrénal," contains cases of true suprarenal pseudohermaphroditism, which are far more frequently of the feminine type, that is, the gonad is the ovary. Masculine pseudohermaphroditism also occurs in this group, but is rare.

Group II, "le virilisme surrénal," embraces cases occurring after birth in the prepuberty period, leading to virilism. This condition is

2. Neugebauer, F. L.: Hemaphroditismus beim Menschen, Leipzig, W. Klinkhardt, 1908.

3. Bullock, W., and Sequeira, J. H.: On the Relation of the Suprarenal Capsules to the Sexual Organs, Tr. Path. Soc. London **56**:189, 1905.

4. Gallais, Alfred: Le syndrome génito-surrénal; étude anatomo-clinique, Thèse, Paris, 1912.

the most common and is found most frequently in girls. It gives rise in varying degrees to symptoms of abnormal development of the body with pubertas praecox (sexual precocity), obesity, hypertrichosis and hypertrophy of the clitoris. When this condition occurs in boys, pubertas praecox and obesity are present together with an accentuated virilism. The sexual precocity may be distinguished from ovarian and pineal precocity by the heterosexual hair, and the adiposity from that of pituitary lesions (Froehlich's syndrome) by the sexual precocity (Oppenheimer and Fishberg [5]).

Group III, "la forme menstruelle," includes cases occurring in women in adult life during the years of menstrual activity. Women with this condition show amenorrhea, obesity, hypertrichosis of the masculine type, enlargement of the clitoris and a frequent change of attitude toward the male type. That this group is small is brought out in a recent paper of Crosbie and Smith [6] concerning a woman who showed typical changes in secondary sex characteristics in relation to an adenoma of the suprarenal cortex. This case they believed to be only the third or fourth authentic instance on record in the Gallais third group, i. e., the adult in the child-bearing period. It is of great interest to note that removal of the tumor effected a reversion to the normal female habitus. More recently Bauer [7] reported the case of a woman 35 years of age apparently belonging to this group. Over a period of one and one-half years she gradually became more obese, began to show hypertrichosis, masculine in type, and had an associated amenorrhea. The sexual instinct disappeared. Gynecologic findings were normal. The blood pressure ranged from 175 to 185 systolic and was 110 diastolic. The woman was operated on for a suprarenal tumor, but none was found. After a short period of time she died, and autopsy revealed normal suprarenal glands with a narrow lipoid zone. The hypophysis was normal, and the kidneys showed slight arteriosclerosis (Bauer [7]). Adult men seldom show the sexual and somatic changes seen in children and in women. According to Rolleston [8] there is only one authentic recorded case of feminism occurring in an adult man with a tumor of the suprarenal cortex.

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5. Oppenheimer, B. S., and Fishberg, A.: The Association of Hypertension with Suprarenal Tumors, Arch. Int. Med. **34**:631, 1924.

6. Crosbie, A. H., and Smith, L. W.: Primary Tumors of the Suprarenal Capsule with Especial Reference to Adrenal Virilism, J. Urol. **19**:241, 1928.

7. Bauer, Julius: Ueber function des gesamten Nebennieren system ohne anatomischen Befund, Wien. klin. Wchnschr. **43**:582, 1930.

8. Rolleston, Humphrey: The Manifestations of Primary Tumors of the Adrenals, West London M. J. **31**:105, 1925.

Group IV, "la forme obstetricalle," includes cases occurring during the period near and after the menopause. Here the clinical picture is indistinct. Adiposity is commonly present, and hypertrichosis may or may not manifest itself.

As emphasized by von Gierke,[9] changes in the suprarenal glands are not uniform in the single groups, nor can specific changes be made out in connection with certain symptoms. Likewise, all changes that have commonly been observed in connection with disturbed sexual development, hyperplasias, adenomas and hypernephromas, may also occur without malformations of the genital organs and clinical genital symptoms. Since, in certain instances, symptoms have disappeared with removal of the tumor, there is little room to doubt that morphologic changes in the suprarenal glands do at times and in some as yet unknown manner cause changes in the genital system.

Influence of the Bisexual Character of the Ovary on Development of Pseudohermaphroditism.—While the determination of pseudohermaphroditism is a very difficult problem, it is interesting to speculate on the possible influence of the bisexual character of the ovary on the development of such states. In origin and early development the ovary and the testis are identical. The medulla of the ovary develops from the primary sex cords arising from the germinal epithelium, and furnishes a complete homologue of the seminiferous tubules in the male. The ovarian cortex develops later from the cords of Pflüger, for which the male gonad never forms normally any homologue. The bisexual potentialities of the ovary are well illustrated in the female bird, which is peculiar in that the left gonad alone matures to form the ovary, while the right gonad persists in a rudimentary state and to some extent in an embryonic condition. This situation was made the basis of significant investigations by Domm.[10] If the left ovary is removed either in young or sexually mature fowls, the right rudimentary gland, in by far the largest number of instances, forms a testis-like body. At times an ovary or an ovotestis develops, such cases being regarded as evidence of accompanying formation of the ovarian cortex of the right gonad before the influence inhibitory to the right cortical development began to operate. On the left, if a small portion of medullary tissue remains at the time of removal of the gland, a testis-like body may develop from that residue; if a portion of cortical substance also remains, an ovary or ovotestis may be formed. There is a distinct masculinizing effect on the accessory organs of reproduc-

9. von Gierke, E.: Ueber Interrenalismus und interrenale Intoxikation, Verhandl. d. deutsch. path. Gesellsch. **33**:449, 1928.

10. Domm, L. V.: New Experiments on Ovariotomy and the Problem of Sex Inversion in the Fowl, J. Exper. Zool. **48**:31, 1927.

tion and other sexual characteristics in the presence of the testis-like gonad that forms from the rudimentary right gonad after removal of the left ovary. In an analysis of the biologic factors involved in this situation, Lillie [11] stated, "with respect to endocrine organization the female thus appears essentially as an hermaphrodite in which the masculine component is never extinguished but merely quiescent." To quote Lillie further, "the evidence for the bisexual character of the female is as conclusive for mammals as for birds, and, while the experimental evidence is not complete, points to the same conclusion that it is the female in mammals as well as in birds that possesses bisexual characteristics." The sterile free martin in cattle studied extensively by Lillie [12] is the female of two-sexed twins. It is zygotically a female, modified by receiving through anastomosis of blood vessels of the two placentae the sex hormone of the male twin, which, circulating in both individuals, results in producing an organism with male gonads and internal genitalia approaching the male type, but with female external genitalia. The cortex of the ovary does not develop in such a female, being suppressed by the male sex hormone. Lillie stated that here "a gonad with a primary female determination may form a structure which is morphologically a testis through suppression of the cortex and overdevelopment of the medullary cords under the influence of the male sex hormone." The resulting situation indicates that "sex in mammals cannot be diagnosed by character of gonads alone. The unexpected result is reached that the external genitalia and the mammary gland are more reliable criteria of female sex than the internal parts."

In a discussion of the present case, Dr. C. R. Moore suggested that the anatomic structure presented by the free martin is curiously like that of the masculine pseudohermaphrodite reported in this paper. The influence that may have brought about a suppression of the ovarian cortex in early fetal life is entirely speculative. It may be that the development of the suprarenal hyperplasia and the suppression of the ovarian cortex were conditioned by the same force. Mathias [13] believed that the primary rôle in the genital maldevelopment belongs to the suprarenal cortex and calls the condition "interrenalismus," while von Gierke [9] uses the term "interrenal intoxikation."

In the person under discussion, the gonad during embryonic life apparently secreted sufficient hormone to influence the development of

11. Lillie, F. R.: The Present Status of the Problem of "Sex Inversion" in the Hen, J. Exper. Zool. **48**:175, 1926.

12. Lillie, F. R.: The Free Martin: A Study of the Action of Sex Hormone in the Fetal Life of Cattle, J. Exper. Zool. **23**:371, 1917.

13. Mathias, E., and Petzal, E.: Eine Weitere Beobachtung von Interrenalismus, Klin. Wchnschr. **5**:2313, 1926.

the vas deferens and a rudimentary epididymis, but except for the patient's extreme height, it is difficult to determine any evidence of male sex hormone secretion in extrauterine life. The patient seemed sexually neutral, physiologically as well as in her behavior. This is of particular interest in view of the large number of cells resembling Leydig cells observed in the testicle. As brought out by Moore,[14] the rôle of the Leydig cells in the production of the male sex hormone is by no means settled. It seems probable that they are not of the extreme importance commonly attributed to them.

Krabbe[15] did not believe that the cases of suprarenal tumor or suprarenal hyperplasia associated with virilism or pseudohermaphroditism prove any especial connection between the suprarenal glands and sexual development, and that this association may be just as well or better explained by the development of early embryonic life. He postulated that the male portion of the ovary, being intimately associated with the development of the suprarenal gland in the beginning stages, is absorbed in some instances by the gland and developed into a part of its structure. Later development and secretion of these misplaced cells cause male characteristics to develop in the female, bringing about a state of virilism or feminine pseudohermaphroditism.

Among the authors other than those cited whose papers on virilism and pseudohermaphroditism are valuable may be noted Glynn,[16] Brutschy,[17] Collett[18] and Scabell.[19]

Previously Recorded Cases of Pseudohermaphroditismus Masculinus Externus Associated with Hyperplasia of the Suprarenal Cortex.—On reviewing the literature, the recorded case appears to be the fourth of pseudohermaphroditismus masculinus externus associated with hyperplasia of the suprarenal cortex and the second such case occurring in an adult.

Brutschy[17] in 1920 reported the occurrence of a bilateral hyperplasia of the suprarenal glands and an accessory suprarenal gland in a 14 day old infant dying of an acute gastro-intestinal disturbance. The external genitalia were feminine in type with two labia, a small

14. Moore, C. R.: The Biology of the Mammalian Testis and Scrotum, Quart. Rev. Biol. **1**:4, 1926.

15. Krabbe, K. H.: The Relation Between the Adrenal Cortex and Sexual Development, New York M. J. **114**:4, 1924.

16. Glynn, E. E.: The Adrenal Cortex, Its Rests and Tumors, Its Relation to Other Ductless Glands, and Especially to Sex, Quart. J. Med. **5**:157, 1911.

17. Brutschy, Paul: Frankfurt. Ztschr. f. Path. **24**:240, 1920.

18. Collett, Arthur: Genito-Suprarenal Syndrome (Suprarenal Virilism) in a Girl One and a Half Years Old, with Successful Operation, Am. J. Dis. Child. **27**:204, 1924.

19. Scabell, Albert: Deutsche Ztschr. f. Chir. **185**:1, 1924.

clitoris and a flat vaginal pit, but no vagina. The internal genitalia consisted of two testicles which lay on either side in the proximal part of the inguinal canal. On the right testicle lay a small mass of accessory suprarenal tissue. Brutschy described a hard muscle-like mass that lay behind the neck of the bladder and into which led two long canals. There was no evidence of uterus or of tubes. The only other abnormal findings were a split uvula and an accessory spleen.

Krabbe [20] in 1924 described, in a new-born child who lived only fifteen hours, external genitalia that were essentially feminine. Internally on the right a small testis had descended into the labium. No testis was present on the left, but in the abdomen, apparently occupying the place of a second testis, there was a tumor of suprarenal cortex tissue which showed no division into the characteristic zones. No rudimentary uterus was present. In the testis and epididymis there were inclusions of cells that resembled those of the suprarenal cortex. Krabbe called attention to the fact that the interstitial cells of the testis may resemble closely the cells of the suprarenal cortex. The suprarenal glands themselves were small and of essentially normal structure. The infant presented in addition spina bifida, paralysis of both lower extremities and clubfeet.

Apparently the first reported case of pseudohermaphroditismus masculinus externus with hyperplasia of the suprarenal cortex in an adult was described by von Gierke [7] in 1928. A 62 year old woman had never menstruated and, although married, was childless. There had never been the least doubt concerning her sex. She underwent an operation for double inguinal hernia. In both hernial sacs were found bodies that macroscopically and microscopically resembled testicles. The ductus deferens was typical. Fourteen days following operation the patient died of pulmonary embolism. Necropsy disclosed a body with feminine distribution of hair, palpable firm breasts and external genitalia of entirely feminine appearance with large and small labia and a small clitoris. The vagina was 3 or 4 cm. long. The spermatic duct proceeded from the inguinal canal to its normal position behind the bladder, where there was also a microscopic seminal vesicle containing only desquamated cells and no spermatozoa. The ducts opened into the upper end of the vagina. There was present a structure that may have been a rudimentary prostate. The breasts showed microscopically the picture of a virgin mammary gland. There were adenomas of both suprarenal cortices. Neither a clinical record of the blood pressure nor an anatomic description of the condition of the heart or of the blood vessels was included in the report.

20. Krabbe, K. H.: Ferholdet Mellein Binyrebarktumores og Pseudohermaphroditisme, Hospitalistid. **67**:651, 1924.

THE RELATION OF THE SUPRARENAL HYPERTROPHY TO THE HYPERTENSION

Hypertension has been observed as a concomitant of hyperplasias, adenomas and hypernephromas of the suprarenal cortex, as well as of hyperplasias and chromaffin cell tumors of the medulla. Oppenheimer and Fishberg [5] believed that, in certain instances, at least, there is a causal relationship between the hyperplasia or tumor and the hypertension. They cited as evidence thirteen cases recorded in the literature and added two of their own, one with necropsy and one in which the diagnosis seemed very probable, in which no anatomic cause other than a demonstrable suprarenal tumor could be brought forward in explanation of the hypertensive condition. Particularly interesting are two cases of Volhard's quoted by Fishberg in which the clinical picture was that of diffuse nephritis with albuminuria. In both instances after the removal of a hypernephroma, the hypertension disappeared. Convincing also are coincident findings of hypertension and suprarenal tumor in children with no other demonstrable lesion to which the hypertension might be attributed. These authors also bring forward considerable anatomic evidence from series of cases reported in the literature that "diffuse hyperplasia and circumscribed adenoma formation in the suprarenal cortex are exceedingly common in persons suffering from hypertension whether it is nephritic or essential in type." More recently Fishberg [21] brought the literature on the subject to date, adding a case reported by Strauss [22] in which a hypernephroma in an adult woman was accompanied by both virilism and hypertension for which there was no other demonstrable cause. He also cited four cases in which hypernephroma in children has been accompanied by both pubertas praecox and hypertension. Other series of cases are noted in which hyperplasia of the suprarenal medulla has been observed in connection with hypertension. In a critical review of the literature, the author traced the development and lack of support of the conception that the hypertension is due to hyperepinephrinemia. The theory that the cortex plays some rôle in the production of epinephrine is not proved, and the presence of epinephrine in the blood of hypertensive patients has never been satisfactorily demonstrated, although the epinephrine content of the suprarenal glands may be increased in conditions with high blood pressure such as hypertension and nephritis

21. Fishberg, A. M.: Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1930.

22. Strauss, H.: Ueber Hirsutismus und Virilismus suprarenalis, Deutsche med. Wchnschr. **52**:2112, 1926.

(Wells [23]). Rabin [24] recently reported a chromaffin cell tumor (pheochromocytoma or paraganglioma) of the suprarenal medulla, collecting reports of thirty such tumors from the literature and summarizing all of the available information concerning the related clinical histories and observations at necropsy. It is significant to note that in nine of the thirty cases and in his own case there was present hypertension independent of renal disease. In two additional cases no clinical reports were available, but there was pathologic evidence of hypertension. Paroxysmal hypertension was present in two other instances. In presenting a case of paraganglioma with diffuse arteriosclerosis and arteriolosclerosis, Biebl and Wichels [25] attributed the condition to a prolonged overproduction of epinephrine, concluding that epinephrine sclerosis in man differs for some reason from experimentally produced epinephrine sclerosis in animals. It seems more probable that the sclerotic changes observed by these authors were present as a result of the prolonged hypertension.

As in the production of the "syndrome genito-surrénal," it is not known why by far the larger percentage of suprarenal tumors fail to give rise to hypertension. Fishberg [20] stated that "it seems possible that a disturbance in the relations between the suprarenals and other organs of internal secretion results in some unknown way in the vasoconstriction which produces the hypertension." At present knowledge concerning the relation of the suprarenal glands both to sexual disturbances and to hypertension is speculative.

THE PINEAL GLAND

Serial sections through the region of the pineal gland of the patient failed to disclose the presence of pineal tissue. In a discussion of changes in the pineal gland, Horrax and Bailey [26] pointed out that the chief theory concerning the function of the pineal gland is that a secretion from this organ inhibits puberty, and that at the time of puberty involutional changes in the gland inhibit the secretion, thus allowing sexual characteristics to develop. Destructive lesions of the pineal gland are known at times to be associated with precocious puberty in boys. No such proved case exists in association with precocious

23. Wells, H. Gideon: Chemical Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1925.

24. Rabin, C. R.: Chromaffin Cell Tumor of the Suprarenal Maculla (Pheochromocytoma), Arch. Path. **7**:228, 1929.

25. Biebl, Max, and Wichels, Paul: Physiologische und pathologische anatomische Betrachtungen im Anschlusz an einin Fall von Paraganglom beider Nebennierin, Virchows Arch f. path. Anat. **257**:182, 1925.

26. Horrax, Gilbert, and Bailey, Percival: Pineal Pathology, Arch. Neurol. & Psychiat. **19**:394, 1928.

puberty in girls. On the other hand, as these authors showed, such tumors may be present with failure of development of precocious puberty. Zandren [27] in 1921 reported an instance of absence of the pineal body in a boy 16 years old. The child had developed normally to the age of 10, but none of the phenomena of puberty followed. The thyroid gland and the hypophysis seemed normal, but the structure of the testicle corresponded to that of a child of 2 years. Zandren postulated from this case that the main function of the pineal body is to initiate rather than to inhibit puberty. If the tumor of the pineal body is a pinealoma or an adenoma, it may be argued that an increased secretion initiates a precocious puberty, thus lending support to Zandren's theory. To quote Horrax and Bailey,[26] "unfortunately for this theory not all the tumors associated with the pubertas praecox are pinealomas, many are teratomas, and one might point again to similar tumors unaccompanied by precocious puberty." Further complicating the picture, the same authors reported a case in which a ganglioneuroma developing from the anlage of the pineal gland completely replaced the structure, no cells resembling the normal structure of the pineal body being present. The patient, however, a man 40 years old, attained a normal physical, mental and sexual development. Krabbe [28] described the occurrence in a female infant, 1 year old, of a pineal gland that had been transformed into a pouch of neuroglia with thin walls and without any sign of pineal cells. The infant did not present any remarkable symptoms except a hydrocephalus and especially no signs of a precocious puberty. Krabb [28] was inclined to discredit the suggestion that absence of the pineal gland may occur in man, because he had noticed that when the brain is taken away from the cranium, the gland often becomes detached, the organ remaining hanging by the vena magna galeni. Because of the coexisting congenital abnormalities in the instance recorded in this report, it is not possible to speculate on the possible significance of the apparent absence of the gland as lending support to either of the theories concerning its function. The incident is recorded as a part of a most extraordinary clinicopathologic picture which in the light of present knowledge cannot be explained.

THE LYMPHOID TISSUES

The extensive hyperplasia of the lymphoid tissues in the wall of the intestine, the mesenteric lymph nodes and the malpighian bodies

27. Zandren, Sven: A Contribution to the Study of the Function of the Glandula Pinealis, Acta med. Scandinav. **54**:323, 1921.

28. Krabbe, K. H.: The Pineal Gland, Especially in Relation to the Problem on Its Supposed Significance in Sexual Development, Endocrinology **7**:379, 1923.

of the spleen is of peculiar interest. Brenner,[29] in a recent paper, accumulated considerable evidence that the site of the essential lesion in Addison's disease is the suprarenal cortex. He brought out the fact that in many cases of Addison's disease, due either to atrophy or to tuberculosis, there is present a status thymicolymphaticus, a generalized hyperplasia of lymph glands or, at times, a lymphoid infiltration of the thyroid gland. Wells [30] pointed out that marked lymphoid infiltration of the thyroid gland is particularly conspicuous in cases of Addison's disease associated with selective destruction of the suprarenal cortex with relatively intact medulla. Jaffe [31] stated that "the newer evidence, including our own work on lymphoid regeneration following suprarenalectomy, supports the view that the lymphoid hyperplasia both in Addison's disease and status lymphaticus is dependent upon insufficiency of the interrenal system (suprarenal cortex)." Marine, Manley and Baumann [32] added further supporting evidence that impaired function of the suprarenal cortex is responsible for thymic and lymphoid hyperplasia. In view of these recent observations, the lymphoid hyperplasia in the case under consideration may or may not be significant, but is of interest, occurring as it does in the presence of a marked increase of both cortical and medullary suprarenal tissue.

SUMMARY

The case of a woman who died at the age of 26 years from a cerebral hemorrhage is reported. Clinically her condition had been diagnosed as chronic diffuse nephritis, hypertension, hypogonadism and infantilism. Postmortem examination disclosed a marked hyperplasia of suprarenal tissue associated with pseudohermaphroditismus masculinus externus, marked cardiovascular changes, apparent absence of the pineal gland and an extensive hyperplasia of the lymphoid tissue in the wall of the intestine, the mesenteric lymph nodes and the malpighian bodies of the spleen. The relationship of the suprarenal hyperplasia to the anomalous development of the genital organs and to the hypertensive condition is discussed.

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29. Brenner, O.: Addison's Disease with Atrophy of the Cortex of the Suprarenals, Quart. J. Med. **22**:121, 1928.

30. Wells, H. Gideon: Addison's Disease with Selective Destruction of the Suprarenal Cortex, Arch. Path. **10**:499, 1930.

31. Jaffe, H. L.: The Influence of the Suprarenal Gland on the Thymus, J. Exper. Med. **40**:325, 619 and 753, 1924.

32. Marine, David; Manley, O. T., and Baumann, E. J.: The Influence of Thyroidectomy, Gonadectomy, Suprarenalectomy, and Splenectomy on the Thymus Gland of Rabbits, J. Exper. Med. **40**:429, 1924.

MALIGNANT HEMANGIOMA OF THE LUNG WITH MULTIPLE VISCERAL FOCI

REPORT OF A CASE *

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At the Babies' Hospital, where over 5,900 autopsies are on record, no primary neoplasm of the lung had been seen until the case reported in this paper was studied in December, 1930. Metastases in the lungs secondary to embryonal adenosarcoma of the kidney had been observed in four instances. In 1903, Baumann and Bainbridge [1] reported a case of primary sarcoma of the lung at the Great Ormond Street Hospital for Sick Children, where the records from January, 1860, described no other case. Their patient was a girl 3 years and 11 months old. The extreme rarity of primary pulmonary neoplasms in young children and the interesting type of tumor presented by this patient warrant a detailed report.

REPORT OF CASE [1a]

History.—E. B. was admitted on Dec. 3, 1930, at the age of 4 months and 20 days. She died the following day. The family history was negative. The child was born at term, weighing 7 pounds and 10 ounces (3.23 Kg.), and was a "blue baby" for a short time. She was breast-fed for three and a half months, and then was given diluted milk of grade A. Her development was normal, and she sat up at 4 months. When she was from 7 to 8 weeks old, wheezing respiration with attacks of groaning and cyanosis were noted, and were supposed to result from a cold. The attacks were more frequent after eating and lasted from fifteen minutes to four hours. When the child was 4 months old, Nov. 14, 1930, Dr. Kernan made a bronchoscopic examination at the New York Hospital. His report on the examination follows. "The bifurcation and mouths of the main bronchi showed distortion by pressure from the outside. The left bronchus was decidedly more deformed than the right. The mucous membrane was extremely congested. Both bronchi could be seen for a considerable way down their course and no foreign body was seen. Their walls were extremely collapsible and appeared to come in contact when the baby coughed, completely closing the lumen. A very considerable amount of thick mucus material was aspirated. It was thought that there was enlargement, from some cause, of a lymphatic node about the bifurcation of the trachea, producing the distortion of the lumen mentioned. This, with the accumulation of secretion in the bronchi and the collapse of the trachea and the bronchi on coughing, would account for the accumulation of

* Submitted for publication, April 15, 1931.

* From the Babies' Hospital and the Pediatric Department of Columbia University College of Physicians and Surgeons.

1. Baumann, E. P., and Bainbridge, F. A.: Lancet **1**:520, 1903.

1a. Dr. John Kernan consented to the publication of this case.

secretion in the child's lungs and the consequent attacks of dyspnea and cyanosis. Postural drainage is suggested, also atropine in small doses, also x-ray exposure to glands."

A quantity of mucus was removed, after which there was improvement. However, the wheezing returned, and Dr. Kernan sent the child to the Babies' Hospital for a second bronchoscopy. Physical examination showed a well developed and well nourished infant with telangectases on the left side of the face and scalp, a large liver, dulness over the upper lobe of the right lung and hyperresonance over the other lobes, with faint breath sounds, especially over the upper lobe of the right lung. The respirations suggested tracheal obstruction. The mucous membrane of the lower lip was dark purple and shiny; an irregular mottling spread to the lower gum. There were a few moist râles over both lungs, but most of the noises seemed to be transmitted from the throat. The heart was normal. The liver reached the level of the umbilicus, and the spleen was not felt. On admission of the patient the diagnosis was tumor of the lung.

Roentgen examination of the chest was interpreted by Dr. Caffey as showing "the right upper lung field completely obscured by a dense, even shadow with poorly outlined lower borders rather than the usually sharply outlined interlobar fissure. The trachea was displaced markedly to the left. The left lung field appeared normal." Dr. Kernan's note on the result of the second bronchscopy reads: "Displacement of the carina and intensely inflamed and swollen bronchial mucosa especially on the left side. It is thought there is still pressure on the trachea and bronchi from large glands accompanied by bronchitis and noticeable collapse of the trachea and bronchi on expiration, explaining the emphysema." Following the bronchoscopy the child had great difficulty in breathing, and respirations ceased several times, being started again by vigorous methods of artificial respiration, administration of epinephrine hydrochloride, etc. The child ceased breathing after repeated attacks of this type in which there was respiratory failure. Dr. W. R. Williams permitted me to examine the x-ray films taken from Oct. 17 to Nov. 26, 1930, at the New York Hospital. At that time the shadow in the upper lobe of the right lung was evident. On November 7, at the New York Hospital, the red cells numbered 3,320,000 and the leukocytes 7,560, with polymorphonuclears 51 per cent and lymphocytes 49½ per cent. The hemoglobin was 60 per cent.

Autopsy.—Autopsy was performed by Dr. Beryl H. Paige. The body was that of a normally developed, moderately well nourished, white female infant. On the left cheek and neck were dilated vessels, and in the lower lip were two small hemangiomas, one on each side of the midline. A small umbilical hernia was present. Permission was given for a thoracic incision only.

The left pleural cavity was free from fluid and adhesions. In the right there were dense fibrous adhesions between the parietal pleura and the visceral pleura covering the upper lobe posteriorly. The heart, esophagus, thyroid gland, pancreas and kidneys were normal. The thymus gland weighed only 6 Gm. The larynx contained much mucus, and the wall showed injection in a narrow zone 5 mm. wide. The mucosa in the lower portion of the trachea showed slight injection, but the wall was free from exudate. In the right main bronchus there was a large amount of mucoid material and slight injection was noted in the proximal 5 mm. of the mucosal wall, while immediately above the division several blackish-red areas (hemangiomas), from 2 to 3 mm. in size, lay in the mucosa. In the left main bronchus there was also some mucus. The proximal 1 cm. of the mucosa was bright red, and was the seat of an angioma 1 cm. in length (fig. 1*a*), extending around almost the entire caliber of the bronchus.

The upper lobe of the right lung was voluminous, measuring 7.5 cm. in its greatest length. On the posterior surface were numerous fibrous adhesions. On the anterior surface was an incomplete accessory fissure, lying from 0.5 to 1.5 cm. above the lower anterior margin of the lobe. The posterior third of the upper lobe was deep red and fleshy in consistency, but not firm. On the surface the lobules were clearly marked. A vertical zone, 2.5 cm. wide, anterior to this area was moderately emphysematous and pale, and the remainder of the upper lobe was deeper red, but air-containing. The lower and middle lobes were bright pink and well aerated. On section, the cut surface of the posterior part of the upper lobe was sharply differentiated into lobules from 1 to 3 cm. in diameter. (fig. 1*b*). The tissue was dark red and fleshy. In the centers of many of the lobules was a pale gray area about 5 mm. in diameter, and these paler areas surrounded small branches of the bronchial tree. The cut surface of the lower lobe was bright

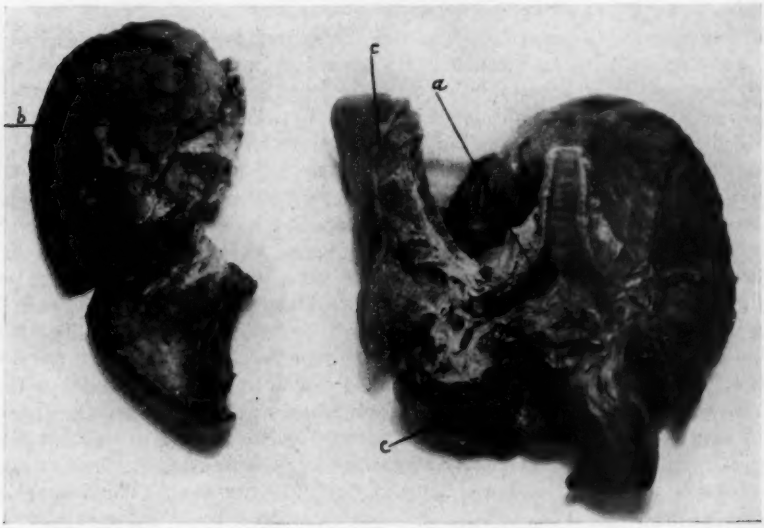

Fig. 1.—At the left is the cut surface of the right lung, showing the lobular outlines and the light central areas of the new growth in the upper lobe (*b*). The left lung, shown at the right, is aerated (*c*). The left main bronchus shows a hemangioma (*a*).

pink and aerated. The left lung was bright pink and well aerated. On the mediastinal margin of the upper lobe near the apex was a lobule over which the pleura showed injection. This lung was normal on section. The tracheobronchial lymph glands were enlarged, the longest being 2 cm. in diameter. They were bright red, soft and discreet.

The spleen weighed 24 Gm. It was deep purplish red, and on section the malpighian bodies were from 1 to 2 mm. in diameter and numerous. The liver weighed 256 Gm. The capsule was normal. The organ was pale, reddish brown and moderately fatty. The gallbladder was normal. In the coils of the small intestine were irregular, deep-purplish areas, where the mucosa showed injection, and the Peyer's patches and the follicles were hyperemic. A mesenteric lymph node was pale gray. The lymph nodes around the pancreas

were deep red, discreet and less than 1 cm. in width. The suprarenal glands were of average size. The cortices were pale yellow, and the central zone appeared as a fine, reddish-brown line. Adherent to the hilus of the right gland was a circumscribed flattened mass of deep-red tissue resembling the lymph glands around the pancreas. One ovary appeared normal, and the other contained several cysts.

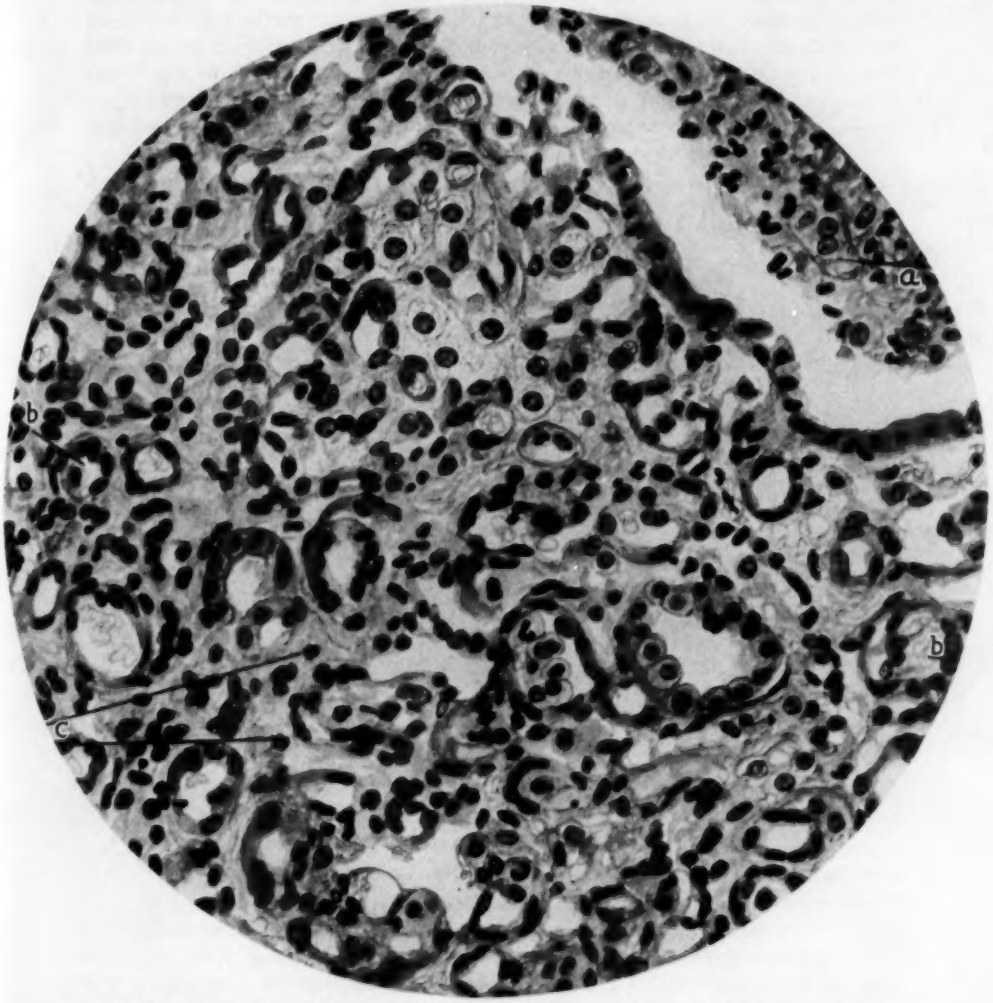

Fig. 2.—A section of the neoplasm in the upper lobe of the right lung, showing bronchiole containing purulent exudate (*a*), vascular channels lined by endothelial cells (*b*), and mitoses in endothelial cells (*c*).

Microscopic Examination.—It would hardly have been possible to identify a section of the upper lobe of the right lung as lung if it had not been for the bronchioles filled with purulent exudate (fig. 2*a*). Around them were no normal alveoli, only masses of blood vessels the lining of which was a single layer of endothelial cells, cuboidal in many places, flattened in others. Their nuclei

were vesicular and hyperchromatic, and a few mitoses were seen. Such vessels contained red blood cells. Between them there was no stroma, merely a basement membrane that stained black with the Weigert-van Gieson stain. These vessels or channels varied in size, but they were capillaries (fig. 2*b*). There were fields in which the growth was more solid and less vascular, the cellular buds not having become canalized. In places the pulmonary alveoli and bronchioles had been compressed to mere slits; in others they were less compressed and were lined with cuboidal (embryonal type) epithelium, but in most fields of the solid tumor no trace of them remained. Mitoses were most common in the solid fields (fig. 2*c*). The veins and arteries in the connective tissue septums between the lobules were filled with red cells. A section taken from the margin, or youngest

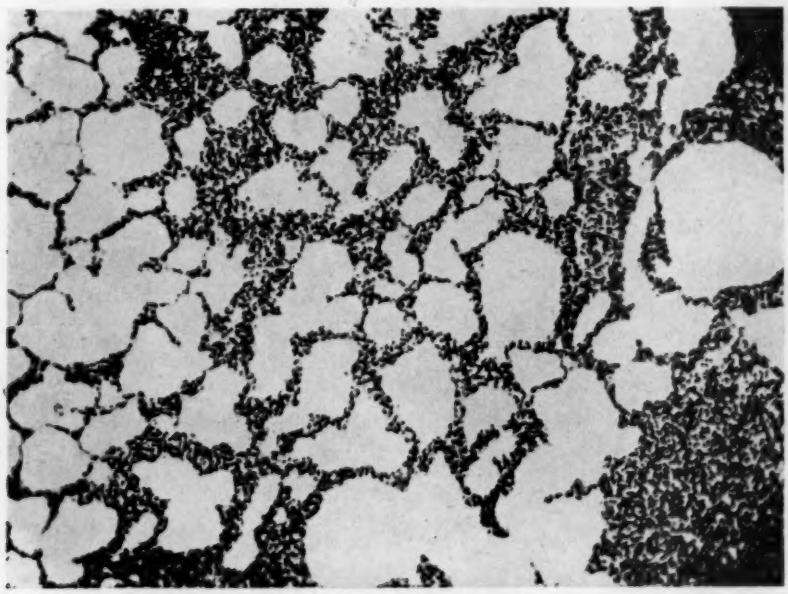

Fig. 3.—A section of the upper lobe of the right lung, showing progressive invasion through the alveolar walls at the edge of the neoplasm.

part, of the tumor showed large areas of cellular growth with little tendency to the formation of blood channels, but much more variation in the size and shape of the nuclei. Many were large, irregular and hyperchromatic. The tumor was growing or progressing through the alveolar walls, thickening them and compressing the alveoli (fig. 3). The invasive malignancy of the new growth was marked in the lung.

The mucosa of the right bronchus was widened, and the newly formed capillaries, filled with red cells, extended almost to the covering epithelium. There were also areas of hemangioma in the mucosa, between the mucous glands, and these extended through the muscularis mucosae into the submucosa and into the connective tissue between the cartilage plates, then into the perichondrium almost to the muscularis, which was not invaded. The newly formed vessels were lined with cuboidal endothelium and contained red cells. There were also solid buds of endothelial cells, not as yet canalized. It seemed plain that the bronchial wall

became invaded by the neoplasm from the parenchyma of the lung, the lobules of angioma becoming largest in the mucosa, where the loose-meshed tissue offered less resistance to proliferation.

In the small intestine, the covering epithelium of the villi was intact, and some villi contained congested capillaries. The mucosa proper contained areas made of small vessels filled with red cells and lined with cuboidal endothelial cells. These vessels or channels were closely packed, and extended through the muscularis mucosae into the submucosa, widening and reddening it. But they stopped at the margin of the circular muscle coat, which was free, as were the lymph follicles in the submucosa. The areas of hemangioma could be plainly distinguished from the uninvolved mucosa, and while solid buds invaded both villi and submucosa,

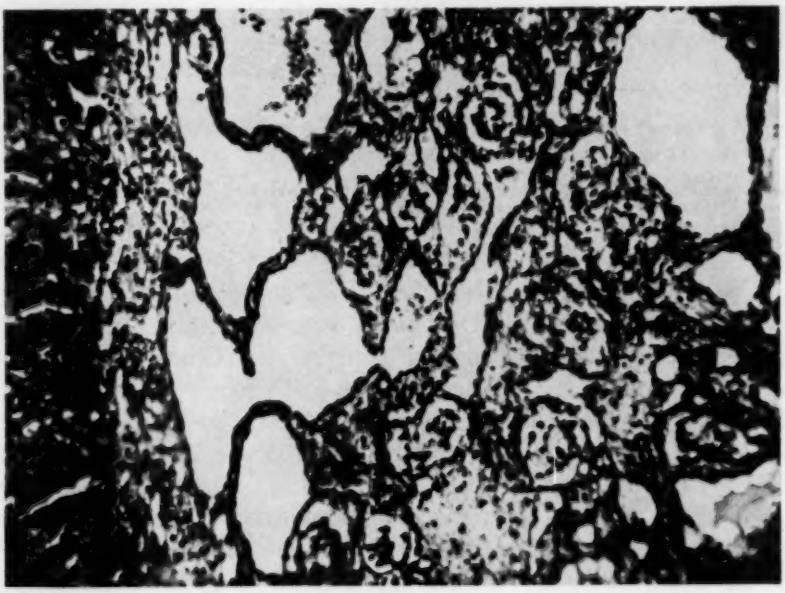

Fig. 4.—A section of the suprarenal gland showing a cavernous type of hemangioma in the medullary zone.

there were places where the outline of the neoplasm was distinct. In the surrounding fat were lobules of tumor tissue.

The cortical cells of the suprarenal gland contained lipoid, and the reticular layer cells were degenerating. In the medullary zone of the suprarenal gland numerous large and small endothelium-lined channels contained erythrocytes and leukocytes. The channels were separated by small strands of connective tissue, their lining cells were flattened, and the picture differed from the rest of the growth because it was distinctly cavernous in type (fig. 4). External to the suprarenal gland were numerous circumscribed lobules of tumor tissue invading and replacing fat lobules, again illustrating the progressive, invasive growth of the neoplasm. A sympathetic ganglion next to the suprarenal gland showed angiomatous invasion.

A few lobules of the pancreas showed hemangiomatous areas, not sharply circumscribed but extending irregularly into the pancreatic lobules. A mass of tissue

taken from the prevertebral area of the upper part of the abdomen showed an uninvaded lymph node and hemangioma apparently replacing fat, as well as uninvaded lobules of adipose tissue. A tracheobronchial lymph gland was free from tumor, but lobules of angioma were replacing fat lobules. The freedom of both thoracic and abdominal lymph nodes from invasion by the tumor was striking. A nodule from the region of the pancreas showed, in addition to pancreas and an accessory spleen, numerous circumscribed lobules of angiomatous tissue and some normal lobules of fat. In the accessory spleen the lymphoid follicles were hyperplastic, the sinuses contained many red blood cells and polymorphonuclears, the capsule was intact, and no evidence of invasion by the tumor was found.

The malpighian bodies of the spleen were large. No tumor was present, nor was there any in the liver or in the kidney. It is to be regretted that no specimen from the skin (lip, cheek, scalp) could be examined, but the restrictions of the autopsy made that impossible.

Diagnosis.—The anatomic diagnosis was: malignant hemangioma of the right lung, bronchi, small intestine, pancreas, suprarenal gland, adipose tissue, abdominal sympathetic ganglion, scalp and lip; fibrous pleural adhesions; acute bronchitis; fatty liver, and cysts of the ovaries.

COMMENT

The gross appearance of the tumor in the upper lobe of the right lung suggested sarcoma. The whole mass was firm, but not hard, shading imperceptibly into aerated pulmonary substance. Microscopically, the lighter areas were those in which the tumor was young, with fewer new vascular channels filled with blood, but with many solid cell masses and compressed alveoli. The extension of the growth into uninvolved lung is well shown in figure 3, which illustrates the proliferating endothelial cells spreading as solid buds along the alveolar walls and into the dilated alveolar ducts as solid masses, sometimes knobbed. In the fat around the right suprarenal gland, the advancing growth showed some similar projections covered by a single layer of endothelial cells. In the lung there were areas in which the cells were arranged in smaller or larger groups or sheets with no canalization, but hardly primitive enough to suggest syncytial masses. These cells had an acidophil cytoplasm, which was granular, and a deeply staining nucleus with occasional mitoses. Close by were narrow blood channels containing red cells, the wall made of a single layer of endothelial cells, which were often cuboidal. These vessels had no stroma between them and compressed the adjacent alveoli so that many of them were mere slits with lining cells that had returned to the embryonal cuboidal type. The growth was malignant and invasive as seen in all the foci, especially the parenchyma of the lung, the intestine, the fat tissue and the sympathetic ganglion. Only in the suprarenal medulla did the tumor assume the cavernous type, while in the adjacent fat it was again formed of capillaries only.

In the literature reports of cases of primary sarcoma of the lung in children are few, and variously designated. Thus Chiari [2] reported a spindle cell sarcoma occurring in the right upper pulmonary lobe of a 14 year old girl. Round cell sarcomas have been described by Hagenbach,[3] Björnsten,[4] Lehndorf [5] and Peters;[6] a lymphosarcoma by Gannon,[7] and a polymorphous cell sarcoma by Acuna and his associates.[8] Rosenblum and Gasul's [9] patient was a girl 29 months old with a large sarcoma of the right lung, but no microscopic details are given. None of these descriptions fits this case, which is so evidently of vascular origin, the type cell being the endothelial cell, and the microscopic picture that of malignant hemangioma. In 1928, Wright [10] collected seven cases of hemangiomatous tumors that formed metastases, and added one of his own. All the tumors occurred in adults, and none was primary in the lung. Four were histologically benign (Borrmann,[11] Ewing,[12] Homans,[13] Shennan [14]), and four were histologically malignant (Langhans,[15] Theile,[16] Jores,[17] Wright [10]). The recent article by Schlopsnies [18] details another case in an adult, the growth involving the spleen, liver and bone marrow. Theile [16] and Jores [17] classified their cases as sarcomatous angioma, and Lubarsch [19] included them both in the group of angioblastic sarcomas or sarcomatous angiomas, for which Borst [20] assumed an origin from endothelial cells that proliferate in the form of buds (embryonal vessels), which in places may become canalized, thus differentiating into vessels the lining cells of which are numerous and

2. Chiari, H.: Anz. d. k. k. Gesellsch. d. Aerzte in Wien, 1877, no. 6, p. 29.
3. Hagenbach, cited by Boschowsky: Frankfurt. Ztschr. f. Path. **9**:239, 1911-1912.
4. Björnsten, cited by Boschowsky (footnote 3).
5. Lehndorf, H.: Wien. med. Wchnschr. **59**:1774, 1909.
6. Peters, C. A.: M. Clin. North America **7**:1823, 1924.
7. Gannon, N. D.: Pennsylvania M. J. **32**:574, 1928-1929.
8. Acuna, M.; Wincour, P., and Orosco, G. P.: Arch. latino-am. de pediat. **23**:605, 1929.
9. Rosenblum, P., and Gasul, A.: Arch. Pediat. **48**:63, 1931.
10. Wright, A. W.: Am. J. Path. **4**:507, 1928.
11. Borrmann, R.: Beitr. z. path. Anat. u. z. allg. Path. **40**:372, 1907.
12. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928.
13. Homans, J.: Ann. Surg. **25**:732, 1897.
14. Shennan, T.: J. Path. & Bact. **19**:139, 1915.
15. Langhans, T.: Virchows Arch. f. path. Anat. **75**:273, 1879.
16. Theile: Virchows Arch. f. path. Anat. **178**:296, 1904.
17. Jores, L.: Zentralbl. f. path. Anat. **19**:662, 1908.
18. Schlopsnies, W.: Virchows Arch. f. path. Anat. **85**:274, 1929-1930.
19. Lubarsch, O.: Pathologische Anatomie der Milz, in Henke and Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1927, vol. 1, p. 2.
20. Borst, M.: Pathologische Histologie, Leipzig, F. C. W. Vogel, 1926.

may appear in several layers. The cells giving rise to this type of neoplasm are angioblasts in their primitive state, endothelial cells in the next stage of their differentiation and potential precursors of sarcoma cells and of blood cells. Wright [10] believed that the tumor that he reported grew from cells less primitive than angioblasts, that is, endothelial cells, but no longer characteristic endothelia, because they had undergone neoplastic change. In the case here reported angioblasts were not present, but the origin from endothelial cells was evident, and the sarcomatous areas were less marked than in those described by Theile [16] and by Schlopsnies.[18] The latter also remarked the lack of involvement of the lymph nodes, and in reviewing the cases belonging in this group of neoplasms, found that the liver was the primary seat in about twenty cases, the spleen in eleven or twelve, the bone marrow in one, the thymus gland in ten and the skin only once. The lung, as the principal focus, has not hitherto been noted.

The case here reported is apparently the first in which the principal or largest mass was in the lung, with smaller foci in other organs. It would be difficult to say which was the primary growth, but the lung was undoubtedly the organ most involved. In this connection Lubarsch [19] raised the question whether in these neoplasms there was a primary growth with metastases, or whether there were not rather independent growths or multiple foci of origin, an "angiomatosis multiplex or even universalis." In the present case multiple foci seem best to explain the condition, for while the foci differed in size, they were of the same age, that in the lung evidently being the most rapidly growing, although the manner of invasion of the perisuprarenal gland and prevertebral fat lobules was as active.

The malignancy of the growth is shown by its local invasiveness in every focus, and by the mitoses in the neoplasmic cells present in these foci. The spidering of vessels in the face was noted when the patient was admitted to the New York Hospital, and a month later at the Babies' Hospital an angioma of the lip, spreading to the gum, was seen. This would seem to argue progressive involvement of the skin.

Only a few cases of multiple hemangiomas occurring in children have been recorded. Stamm [21] described one in a 4 months old infant which involved the skin, muscles, both lungs, right vocal cord, ovaries, small intestine and cerebral cortex, and diagnosed it as angioma simplex. Ramdohr [22] detailed the case of a new-born infant who died of hemorrhage from a tumor on the inferior maxilla and had multiple nodules of angiosarcoma in the skin, lungs and kidneys. The lungs were not

21. Stamm, C.: Beiträge zur Lehre die Gefässgeschwülsten, Dissertation, Göttingen, 1891.

22. Ramdohr, M.: Virchows Arch. f. path. Anat. **73**:459, 1878.

involved in the cases occurring in children reported by Brüchanow,[23] Ernst [24] and von Falkowski;[25] von Falkowski's patient, a boy 2¾ months old, had angiomas of the skin, spleen and liver, which he classified as a peculiar form of mesenchymal benign hamartoma, the result of a systemic disease of the embryonal mesenchyme, a tissue maldevelopment. In Ernst's [24] patient, 2 months and 20 days old, the liver, spleen and skin were the seat of nodules diagnosed as congenital angioma simplex. Brüchanow's [23] patient, 15 weeks old, showed multiple hemangiomas of the skin, the liver and the periosteum of two ribs. Böckelmann's [26] patient, 15 months old, underwent splenectomy for an angiosarcoma of the spleen, and de Haan [27] reported an alveolar angiosarcoma of the liver without metastases in a baby 4 months old. It is apparent that the lungs are but infrequently involved in neoplasms of the group of malignant hemangiomas.

SUMMARY

A case of multiple malignant hemangiomas in an infant, involving the lung, skin, bronchi, pancreas, intestine, suprarenal gland, prevertebral fat and sympathetic ganglion, is described. The principal and largest mass was in the upper lobe of the right lung, a condition not noted in any other reported case. The lymph nodes were not involved in the neoplasmic process.

23. Brüchanow, N.: Ztschr. f. Heilk. **20**:131, 1899.
24. Ernst, P.: Verhandl. d. deutsch. path. Gesellsch. **15**:232, 1912.
25. von Falkowski, A.: Beitr. z. path. Anat. u. z. allg. Path. **57**:385, 1913.
26. Böckelmann: Ueber ein Angiom der Milz; Inaug. Diss., Greifswald, 1906.
27. de Haan, J.: Beitr. z. path Anat. u. z. allg. Path. **34**:215, 1903

EXPERIMENTAL SCARLATINAL NEPHRITIS IN THE DOG*

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The present views on the sequence of the early anatomic changes that underlie certain clinical types of nephritis are largely conjecture. This is due, in part, at least, to the fact that the renal function is so complex and the possible lesions so varied that an accurate correlation of the urinary observations and the renal changes is prevented. It is generally held that abnormalities in the urine as determined by microscopic and chemical analysis are only presumptive evidence of nephritis, since these may be present without demonstrable renal lesions. Even when the urinary observations point to renal changes, they are not a reliable criterion of the location, extent and degree of these changes, because the exact relations between renal structures and their functional activities are imperfectly understood. Therefore, albumin, casts and blood in the urine offer little information as to whether there is a renal structural change or merely a functional disturbance.

My purpose in this paper is to report the results of experiments on animals which were instituted in order to determine as far as possible the relation of the renal structural changes, and to trace their development in correlation with abnormal urinary findings. Experimental nephritis was induced in dogs with (1) living culture, (2) killed culture and (3) the filtered in vivo prepared toxic product of Streptococcus scarlatinae.

EXPERIMENTS

Since nephritis frequently occurs spontaneously in the dog, I used only young animals the urine of which over a period of from ten days to two weeks was free from albumin, casts and other abnormalities, and the renal function of which, as determined by the phenolsulphonphthalein test, was within the normal limits. During the period of observation the animals were kept in metabolism cages to facilitate the collection of urine. Catheterized specimens were not employed; hence the figures in the tables for the volumes of urine are averages only, which were obtained by dividing the total volume of urine of seven days

* Submitted for publication, March 28, 1931.
* From the Department of Pathology, Tulane University School of Medicine.
* A preliminary report appeared in: Proc. Soc. Exper. Biol. & Med. **26**:546, 1929.
* Aided by a grant from the David Trautman Schwartz Research Fund of Tulane University.

by the number of days in the period. Daily examinations of urine were made over a period of from one to three weeks after the administration of the nephrotoxic agent. In the case of dogs that survived several months, the examinations of the urine were made at weekly intervals after the first three weeks. The phenolsulphonphthalein test was repeatedly carried out on all dogs at approximately weekly intervals.

Fourteen young, healthy dogs were employed in the experiments. Nephritis was induced by intraperitoneal and intravenous injections of "living" and "killed" cultures of scarlatinal streptococci and of a "lysate" of these streptococci (prepared after the method of Duval and Hibbard [1]). The dosage of "killed" culture was the entire forty-eight hour surface growth of twelve blood agar slants suspended in from 15 to 30 cc. of sterile physiologic solution of sodium chloride; while the dose of the "lysate" was from 15 to 30 cc. of sterile Berkefeld "N" filtered peritoneal fluid from an immune rabbit that had previously received intraperitoneally the forty-eight hour streptococcal surface growth of twelve blood agar slants. The dosage of "living" culture employed was the forty-eight hour surface growth of three blood agar slants suspended in 10 cc. of sterile water.

The following protocols are representative of the results obtained:

Dog 1.—Dog 1 was a female weighing 5 Kg. During a preliminary period of observation of one month daily samples of urine were found free from abnormal constituents. The animal was given an intraperitoneal injection of 30 cc. of lysate of scarlatinal streptococci prepared in vivo. One hour later the dog vomited and appeared greatly prostrated. On the following day the animal was better, but refused food. Three days after the first injection, the dog ate again and appeared well. Two weeks after the injection albumin appeared in the urine and continued to appear for the remaining period of the experiment. Three weeks after the first injection a second injection of 15 cc. of lysate was given intraperitoneally. Two weeks later a third intraperitoneal injection of 15 cc. of lysate was given. After each injection the dog vomited and appeared very ill for two days. The second and third injections apparently caused greater quantities of albumin to appear in the urine, and after the third injection blood and casts, both fine and granular, were also noted. The dog was found dead in its cage one week after the third injection or approximately two months after the first injection of lysate.

At autopsy there was the usual picture of a severe toxemia in the spleen, heart, liver and kidneys. The kidneys in particular were markedly swollen and generally dark red. On section the cortex presented conglomerate and discrete pinhead-sized and smaller, yellowish-white areas. The glomeruli were discerned as dark red, elevated dots, resembling in many instances petechiae. Because of these hemorrhagic spots near the capsule, the cortical surface of the kidney presented the classic "turkey-egg" spotting.

Microscopically, the outstanding lesions were in the glomeruli, and varied from simple hyperemia of the capillary tufts to rupture and actual hemorrhage into the capsular space.

1. Duval, C. W., and Hibbard, R. J.: J. Exper. Med. **44**:567, 1926.

Dog 3.—Dog 3 was a female weighing 11.1 Kg. During the preliminary period of observation (eight days) the urine remained normal. On January 24, the first intravenous injection of 20 cc. of a suspension of killed scarlatinal streptococci was made. Similar amounts of the killed culture were injected sixteen and twenty-six days later. Albumin, blood and a trace of bile appeared in the urine two days

TABLE 1.—*Urinary Findings in Nonfatal Experimental Nephritis Induced in Dog 3 with Three Intravenous Injections of Killed Scarlatinal Streptococci*

Date	Volume of Urine Excreted in 24 Hours, Cc.	Amount of Killed Culture Injected Intravenously, Cc.	Albumin	Blood	Bile	Casts: Hyaline	Casts: Fine Granular	Casts: Coarse Granular	Phenolsulphonphthalein Excreted, per Cent	Comment
1/24	365	20	0	0	0	0	0	0	67.4	First injection
1/25	270	..	0	0	0	0	0	0	....	
1/26	280	..	+	+	0	0	0	0	....	First clinical evidence of nephritis
2/ 8	350	..	+	0	0	0	0	0	....	
2/ 9	365	20	+	0	0	0	0	0	....	Second injection
2/11	205	..	++	+	0	0	0	0	....	Increased albumin; blood
2/13	500	..	++	+++	+	0	0	0	....	Marked hematuria; bile
2/14	220	..	++	++	0	0	0	0	52.0	
2/15	210	..	+	+	0	0	0	0	....	
2/16	200	..	+	+	0	0	0	0	....	
2/17	215	..	+	0	0	0	0	0	....	Disappearance of blood
2/18	215	..	+	0	0	0	0	0	....	
2/19	520	20	+	0	0	0	0	0	....	Third injection
2/21	180	..	+	0	0	0	0	0	....	
2/22	220	..	+++	++	+	++	++	++	46.7	First appearance of casts
2/23	275	..	+++	+	+	++	++	++	....	
2/27	275	..	+++	+	+	+	+	+	....	Decreased excretion of dye
2/28	90	..	++	0	+	0	0	0	....	Oliguria marked
3/ 2	230	..	+++	0	+	0	0	0	....	
3/ 4	380	..	+	0	0	0	0	0	....	
3/ 5	240	..	+	+	+	0	0	0	....	
3/16	240	..	+	+	+	0	0	0	....	
3/23	130	..	0	0	0	0	0	0	59.3	Diminished excretion of urine
3/24	300	..	0	0	0	0	0	0	....	
3/31	300	..	0	0	0	0	0	0	....	
4/ 5	435	..	0	0	0	+	+	+	....	Reappearance of casts
4/ 8	350	..	+	0	+	+	+	+	....	
4/15	400	..	0	0	0	+	+	+	....	
4/22	250	..	+	0	+	+	+	+	....	Persistence of albumin and casts
5/ 3	200	..	+	0	+	+	+	+	41.2	
5/11	250	..	+	0	+	+	+	+	....	Evidence of chronic nephritis
5/18	Dog was killed. Autopsy revealed acute and chronic nephritis									

after the first injection (see table 1). In addition to albumin and blood, hyaline and granular casts appeared in the urine three days after the third intraperitoneal injection of "killed" culture. These pathologic substances were observed in the urine at every subsequent examination over a period of three months, though the dog was fat and appeared in good health. The animal was killed five months after the first inoculation. The changes observed at autopsy were acute glomerulonephritis, tubular nephritis and interstitial infiltration with lymphocytes. There was no increase in the connective tissue.

Dog 4.—Dog 4 was a female weighing 6.7 Kg. This animal was under daily observation for twelve days prior to the experiment. During this time the urine and the renal function were normal. On January 24, 15 cc. of streptococcal lysate

TABLE 2.—*Urinary Findings in Fatal Experimental Nephritis Induced in Dog 4 with Three Intraperitoneal Injections of "Lysate" of Scarlatinal Streptococci*

Date	Volume of Urine Excreted in 24 Hours, Cc.	Amount of "Lysate" Injected Intraperitoneally, Cc.	Albumin	Blood	Bile	Casts: Hyaline	Casts: Fine Granular	Casts: Coarse Granular	Pus	Phenolsulphonphthalein Excreted, per Cent	Comment
1/24	210	15	0	0	0	0	0	0	0	87.3	First injection; vomited two hours afterward
1/25	260	..	0	0	0	0	0	0	0	....	
1/26	...	..	0	0	0	0	0	0	0	....	
2/ 1	200	..	0	0	0	0	0	0	0	....	
2/ 9	195	15	+	0	0	0	0	0	0	....	Second injection
2/10	210	..	+	+	+	+	0	0	0	66.0	Diminished excretion of dye
2/11	120	..	++	+	+	+	0	0	0	....	Oliguria
2/14	200	..	++	+	+	+	+	+	0		
2/19	130	15	+	+	+	+	0	0	0	....	Third injection
2/21	150	..	++	++	+	+	+	0	0	....	Dog sick and not eating
2/22	70	..	+++	++	+	++	++	++	+	71.5	
2/23	90	..	++	+	+	++	++	++	+	....	Marked oliguria
2/24	Dog was found dead in cage. Autopsy revealed acute hemorrhagic glomerulonephritis										

TABLE 3.—*Urinary Findings in Nonfatal Experimental Nephritis Induced in Dog 11 with Single Intraperitoneal Injection of "Lysate" of Scarlatinal Streptococci*

Date	Volume of Urine Excreted in 24 Hours, Cc.	Amount of "Lysate" Injected Intraperitoneally, Cc.	Albumin	Blood	Bile	Casts: Hyaline	Casts: Fine Granular	Casts: Coarse Granular	Phenolsulphonphthalein Excreted, per Cent	Comment
2/22	600	10	0	0	0	0	0	0	76.0	First injection, animal vomited immediately
2/23	500	..	0	0	0	0	0	0	....	
2/24	200	..	+++	+	+	+	+	+	....	Animal very sick
2/25	230	..	+++	0	+	+	+	+	....	
2/26	530	..	++	0	+	+	+	+	....	Animal eating again
3/ 3	375	..	+	0	+	+	+	+	....	
3/ 4	300	..	+	+	+	+	0	+	....	
3/ 9	170	..	+	+	+	0	0	0	....	
3/16	210	..	+	0	+	+	+	+	64.5	
3/26	210	..	0	0	0	0	0	0	....	
3/28	90	..	+	0	+	0	0	0	....	Marked oliguria
4/ 8	200	..	+	0	+	+	+	0	....	
4/15	185	..	+	0	+	+	+	+	....	
4/22	300	..	+	0	+	+	+	+	61.7	
4/28	280	..	+	0	+	+	+	+	....	
5/10	300	..	+	0	+	+	+	+	....	
5/20	330	..	++	0	+	++	++	++	39.0	Excretion of dye markedly decreased
5/22	290	..	++	0	+	++	++	+	....	
5/28	180	..	+	0	+	++	++	++	....	
6/ 2	280	..	++	..	..	++	++	++	....	Evidence of chronic nephritis
11/20	Dog was killed, six months after injection; at this time it was apparently in good health. Autopsy revealed glomerular and interstitial nephritis									

was injected intraperitoneally. Subsequent injections of lysate in the same dosage were made on February 9 and 19. After each injection the dog vomited and refused food for twenty-four hours. After the third injection diarrhea developed, and the animal was found dead in its cage five days later. Albumin was first noted in the urine six days after the first injection and was present at every subsequent examination. Bile, large numbers of hyaline and granular casts and blood appeared in the urine after the third injection. Three days later the animal died, and at autopsy the kidneys showed diffuse hemorrhagic glomerulonephritis.

Dog 11.—Dog 11 was a female weighing 6.1 Kg. The preliminary period of observation lasted for two weeks, during which daily tests made of the urine revealed no abnormalities. The phenolsulphonphthalein test at this time showed 72 per cent excretion of the dye. On February 22, 10 cc. of streptococcal lysate was injected intraperitoneally. Vomiting occurred immediately. This animal

TABLE 4.—*Urinary Findings in Fatal Experimental Nephritis Induced in Dog 14 with Single Intravenous Injection of "Lysate" of Scarlatinal Streptococci*

Date	Volume of Urine Excreted in 24 Hours, Cc.	Amount of "Lysate" Injected Intravenously, Cc.	Albumin	Blood	Bile	Casts: Hyaline	Casts: Fine Granular	Casts: Coarse Granular	Phenolsulphonphthalein Excreted, per Cent	Comment
4/ 6	500	12	0	0	0	0	0	0	84	First injection; animal vomited
4/ 7	400	..	++	+	+	++	++	++	..	Marked evidence of nephritis
4/ 8	340	..	++	+	+	+	+	+	..	Animal very sick
4/ 9	500	..	+	+	+	+	+	0	..	Animal improved
4/14	200	..	+	0	++	+	0	+	60	Excretion of dye diminished
4/22	210	..	+	+	++	+	+	+	..	Animal not eating
4/24	300	..	++	++	+	++	++	+	..	Severe diarrhea
4/25	200	..	++	+	++	++	++	++	..	Very weak and sick
4/27	Dog was found dead in cage. Autopsy revealed acute hemorrhagic glomerulonephritis									

received only one injection. Albumin, bile, blood, hyaline and coarsely granular casts appeared in the urine forty-eight hours after the injection. Albumin and bile were excreted continuously over a period of four months, until the animal was killed.

Autopsy revealed acute glomerulonephritis and early interstitial leukocytic infiltration as the outstanding renal changes.

Dog 13.—Dog 13 was a male weighing 6.7 Kg. During the preliminary observation (ten days), all samples of urine were free from pathologic constituents. On April 28, 15 cc. of streptococcal lysate was injected intravenously. On the following day albumin and hyaline and granular casts were found in the urine. Thereafter albumin was present in the urine to the end of the experiment. A second injection of 15 cc. of lysate was given intravenously on May 3, five days after the first injection, which failed to cause vomiting or sickness. After May 3 traces of bile and blood were excreted and casts and pus appeared occasionally until June 12, when the dog was killed. The autopsy revealed albuminous and fatty degeneration of the liver and heart and acute glomerulonephritis.

Dog 5.—Dog 5 was a male weighing 6.6 Kg. During the preliminary period of observation (twelve days) the urine was normal. On February 19, 20 cc. of a suspension of living scarlatinal streptococci was injected intraperitoneally. Vomit-

ing and diarrhea occurred one hour later, and the animal appeared ill. The following day the dog was comatose and died. The urine showed great quantities of albumin.

Autopsy disclosed acute glomerulonephritis and a fatty heart and liver.

Dog 7.—Dog 7 was a female weighing 6.8 Kg. The animal was under observation for two weeks prior to experimentation; during this time the urine was normal. Lysate to the amount of 15 cc. was administered by intravenous injection on March 16. The dog vomited shortly after the injection. The following day it appeared normal. On March 18, albumin, hyaline and granular casts and bile appeared in the urine. On March 23, the excretion of phenolsulphonphthalein in two hours was 64 per cent. One month later this test showed 78 per cent excretion of the dye, which is normal, and there were no abnormalities in the urine. The animal was killed, and autopsy revealed acute glomerular and slight chronic interstitial nephritis.

Dog 14.—Dog 14 was a male weighing 13.6 Kg. Prior to the experiment the urine was examined daily for twelve days and found to be normal. On April 6, 12 cc. of lysate was injected intravenously. The animal vomited following the injection. On the second day after the injection, albumin, hyaline and granular casts, blood and bile appeared in the urine. These persisted in the urine to the end of the experiment. The animal was sick throughout the period of observation, and died twenty-one days after the injection of lysate.

Autopsy showed acute hemorrhagic nephritis, fatty liver and hypertrophy and dilatation of the heart.

THE RENAL CHANGES IN STRUCTURE

The acute renal lesion of the experimental scarlatinal nephritis in these dogs was characterized macroscopically by an increase in the size of the kidney, by swelling of the glomeruli, which projected above the cut surface as dark red dots, and by pinhead and smaller, discrete, yellowish-white lineations in the cortical substance and in some instances by a sprinkling throughout the organ of minute hemorrhages (turkey-egg spotting). The gross appearance of the kidney in chronic nephritis in these dogs was that of an organ of normal or slightly under-normal size, in which the consistence was increased and the color pale reddish brown. There were also numerous small retention cysts and cicatricial depressions scattered through the cortical substance.

The earliest microscopic change was an intense engorgement of the capillaries of the glomeruli with often densely packed erythrocytes that appeared as though the hemoglobin had been dissolved out. In many of the capillary tufts the loops were enormously distended with what appeared to be erythrocytic thrombi. Other capillaries were distended by masses of eosin-staining material, which was homogeneous and which apparently was formed from the fused and destroyed red blood cells. Many of these hyaline-thrombosed capillary loops were glued to the wall of Bowman's capsule. In the case of some dead capillary loops, new connective tissue partially or completely cicatrized them. In other glomeruli where the capillaries were not blocked by thrombi, the lumina contained large numbers of mononucleated cells. The nature of these

cells was difficult to determine, since they appeared to be outside of the capillaries in the capsular space; however, in no instance were they of the neutrophil variety. I am inclined to regard them as endothelial cells because of their manner of staining and because of the character of the nucleus, which was definitely vesicular and surrounded with considerable basic-staining cytoplasm. In still other glomeruli extensive hemorrhage was noted, which, in some instances, could be readily traced into the corresponding tubule. Sometimes the hemorrhage into the subcapsular space was so large as to misplace or crowd out the capillary tuft. When blood escaped into the subcapsular space, the red cells fused into a homogeneous, pink-staining mass which often became attached to the capsule. In these masses there commonly occurred connective tissue and an invasion by epithelial cells producing the so-called "crescent." The replacement of the hyalinized capillaries by fibrous tissue produced complete or partial glomerular sclerosis.

The tubular epithelium was not affected until late in the glomerular process; then it became swollen, granular and filled with fat droplets; especially was this the case with the epithelium of the convoluted portion of the tubule. In places the epithelium had desquamated and the tubule had atrophied, and eventually in those instances in which the corresponding glomerulus was destroyed the tubule degenerated. All kinds of casts were demonstrated. A significant feature was the absence of any acute inflammatory lesion in and about the involved tubules.

When a dog had received several injections of streptococcal lysate, and had been allowed to live for six months or longer, and previous examinations of the urine had shown the existence of an acute glomerular nephritis, microscopic study of the kidneys revealed considerable change of a reparatory character in the interstitial connective tissue. In these kidneys there was noted an increase of fibrous tissue in the areas where the greatest damage had occurred to the glomeruli. In such areas of connective tissue many of the tubules were atrophic, and the glomeruli were in various stages of retrogression, some being actually necrosed. Some convoluted parts of tubules in the affected areas appeared larger and others smaller than normal; the larger ones in some instances were even cystic, owing to the mechanical interference with the passage of urine caused apparently by the contraction of the adjacent newly formed connective tissue.

The animals that received the living culture of streptococci showed at autopsy as the outstanding renal lesion focal and diffuse lymphocytic interstitial infiltration. The kidneys also showed a moderate degree of glomerular, but no tubular, change. Few if any neutrophils occurred in the stromal lesion. Streptococci were demonstrable in the stained renal sections and were recoverable in pure culture from the fresh tissue.

CORRELATION OF URINARY OBSERVATIONS AND RENAL DISTURBANCES

The sequence and relation of the renal changes in correlation with the functional disturbances as expressed by abnormal urinary constituents were studied from the commencement of the acute renal lesion until chronic nephritis was well established.

The appearance of albumin and casts in the urine was constant in all the dogs given injections. In most cases albumin and casts occurred within twenty-four hours after the injection of the nephrotoxic agent, while in others these abnormalities were found only after from two to three days (see table 1). In addition to albumin and casts, the majority of the dogs showed blood and traces of bile in the urine, although usually these substances did not appear before the third day following the injection (see table 2).

Four of the acutely nephritic dogs were allowed to live for six months or longer. These animals in two or three months after the third and last injection of the streptococcal nephrotoxin apparently returned to a normal renal function as indicated by the total absence of abnormal constituents in the urine. However, at autopsy there was definite gross evidence of chronic renal changes, which was confirmed by microscopic study.

It is particularly noteworthy that the urinary findings from day to day were a fairly reliable index to the anatomic changes in the kidneys. Blood in the urine invariably meant glomerular hemorrhage, while fine, granular casts foretold serious retrograde changes in the epithelium of the convoluted tubules, which seemed to be dependent on, but always secondary to, lesions of an obstructive character in the glomerular tufts. Here it is of interest to mention that the primary glomerular lesions followed by secondary tubular changes is the reverse of the sequence induced in dogs with uranium nitrate, which, according to MacNider,[2] produces a primary lesion of the epithelial cells of the proximal convoluted tubules.

As early as the second day following the injection of the streptococcal nephrotoxin, the dogs passed urine containing albumin, bile and blood (see table 3). At this time there was usually a marked reduction in the elimination of phenolsulphonphthalein, and this depression of renal function was the result of injury to the glomerular structures and not of injury to the tubular, as was revealed by microscopic study of the kidneys of some of the animals.

The functional changes gradually diminished in severity after from three to four days in dogs that received only one injection of nephrotoxin, and the elimination of phenolsulphonphthalein increased. These expressions of functional improvement occurred pari passu with the

2. MacNider, W. de B.: J. Exper. Med. **49**:387, 1929.

clearing of the glomerular injury. A second and third injection of the nephrotoxin was often followed by urinary abnormalities more severe than those following a single injection (see table 2). However, albumin, blood and casts in marked quantities occurred following the single injection of nephrotoxin. Furthermore, these substances appeared in the urine within a few hours in dogs that had had more than one injection of the nephrotoxin, which might be attributed to a previously induced allergic renal state. Again in these dogs the normal renal function was reestablished much more slowly or the pathologic condition became progressively worse until death. In these animals there was more histologic evidence of glomerular destruction and beginning evidence of retrograde changes in the epithelium of the convoluted parts of tubules. The study of the urinary secretions from the kidneys of these animals permits the deduction that regeneration of tubular epithelium does not occur when the corresponding glomerulus has been destroyed. This may possibly be explained on the ground that the supply of blood to the tubule, which is largely through the efferent branch of the glomerulus, has become cut off by the process in the latter.

COMMENT

The results of the experiments here reported are of special interest, since the renal changes were produced with a nephrotoxin that commonly causes nephritis in man. It is also noteworthy that there is a rather complete correspondence between the experimentally induced renal changes and the nephritis of scarlet fever. In consequence a closer analogy can be drawn to the human disease than is possible when improbable excitants of human nephritis, such as uranium nitrate, have been employed. Furthermore, the scarlatinal nephritis in these dogs afforded the opportunity to determine the relative dependence of the urinary abnormalities on certain of the renal changes. While many investigators have produced experimental nephritis in a variety of animals and with a variety of substances, including pathogenic microorganisms and their products, few, it would seem, have attempted to determine the true relationship of the urinary abnormalities to the structural changes in the kidney when common nephrotoxic substances to which man is subject are employed. In this connection the work by Christian,[3] by Pearce and Eisenbrey[4] and by Underhill, Wells and Goldschmidt,[5] among others, would have been of greater clinical value

3. Christian, H. A.: Tr. Congress Am. Physicians & Surgeons **9**:1, 1913.

4. Pearce, R. M., and Eisenbrey, A. S.: J. Exper. Med. **14**:306, 1911.

5. Underhill, F. P.; Wells, H. G., and Goldschmidt, S.: J. Exper. Med. **18**: 347, 1913.

had they employed nephrotoxic agents that commonly cause nephritis in man. As MacCallum [6] pointed out, such substances as uranium nitrate, tartrates, snake venoms and the like are improbable excitants of human nephritis, and therefore the lesions experimentally produced by these may not be at all comparable with those of human nephritis.

In discussing the manner of production of experimental nephritis, the question of allergy comes up for consideration, because it is claimed that allergic lesions in the kidney are inducible with streptococcal antigens. In this connection it is notworthy that Birkhaug [7] found allergy in a high percentage of rheumatic fever infections obtained with filtrates, autolysates and suspensions of various nonhemolytic streptococci, from which he concluded that there is a common allergenic factor in streptococcal products. Longcope [8] produced specific lesions in the kidney by occasioning in the previously sensitized experimental animal repeated intoxication with protein. Long and Finner [9] succeeded regularly in producing glomerulonephritis by injection of tuberculin into the sensitized experimental animal. Heplar and Simonds [10] reported the results of their work on the experimental production of allergic inflammation in the kidney. In all of the reported instances of experimentally induced allergic nephritis it would seem that the specific lesion has occurred only after repeated injections of the antigenic substance or in animals in which the hypersensitive state existed. Longcope,[11] however, claimed to have produced with a single large dose of foreign protein specific injury to parenchymatous organs, which he ascribed to the gradual splitting of the protein within the animal's body, resulting in the liberation of toxic substances. In this instance, it must be assumed that the allergic reaction was the result of a sensitization of tissue induced by the toxic product first split from the protein. That an allergic reaction accompanied by structural changes may occur simultaneously in the kidney and other organs as well as in the skin is likely in any case in which there exists a specific hypersensitiveness to protein, as has been shown by Gay and Southard,[12] Boughton,[13] Longcope [14] and others.

Bacterial allergy most likely influences the clinical picture in all streptococcal nephritis of man, and particularly the postscarlatinal form.

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6. MacCallum, W. G.: A Text Book of Pathology, ed. 4, Philadelphia, W. B. Saunders Company, 1928, p. 262.
7. Birkhaug, K. E.: J. Infect. Dis. **40**:549, 1927.
8. Longcope, W. T.: J. Exper. Med. **18**:678, 1913.
9. Long, E. R., and Finner, L. L.: Am. J. Path. **4**:571, 1928.
10. Heplar, O. E., and Simonds, J. P.: Am. J. Path. **5**:473, 1929.
11. Longcope, W. T.: J. Exper. Med. **22**:6 and 793, 1915.
12. Gay, F., and Southard, E. E.: J. M. Research **16**:143, 1907.
13. Boughton, T. H.: J. Immunol. **1**:105, 1916.
14. Longcope, W. T.: Arch. Int. Med. **15**:1079, 1915.

In these cases, as shown by Longcope,[15] there are persisting foci of streptococci from which is absorbed a toxic product that on reaching the already sensitized kidneys excites new changes of an allergic nature.

As regards the nephritis reported here I do not believe that allergy could have played any part in the production of the specific renal changes following the first injection of antigen. To explain the nephritis following the primary dose on the basis of an allergic reaction it would be necessary to assume that the animals were already hypersensitive to streptococcal protein. It is not likely that in all of these dogs an allergic state existed because of a previous streptococcal infection. Since the recurrence of acute nephritis in these dogs followed repeated injections of the product of S. scarlatinae, these secondary renal reactions could be regarded as allergic, which would support Longcope's conception of the production of postscarlatinal nephritis in man.

Constant and significant structural changes occurred in the dogs in which nephritis was experimentally produced with scarlatinal streptococci or with the toxic product of these organisms. The lesions were glomerular, tubular and interstitial. As a rule, the glomeruli were primarily affected when the toxic principle was in the form of killed culture or "lysate," regardless of whether the injection was made intravenously or intraperitoneally, while, as previously reported,[16] an interstitial type of lesion occurred in animals which had been inoculated with the living streptococci, and in which a generalized infection had developed. The interstitial lesion was an infiltration of the intratubular tissues with lymphocytic cells. Commonly the neutrophils were absent or only few; however, in some of the more advanced stromal lesions they occurred, but were not as numerous as the lymphocytic cells. Associated with the interstitial lesions were viable streptococci, which were readily demonstrable in stained sections and recoverable in pure culture from the fresh tissues. The absence of fibroblasts or of any other evidence of stromal activity in the early interstitial lesion is significant since it indicates that the lymphocytic infiltration was a true reaction of the host to the injurious agent and therefore not reparatory. From this it may be inferred that acute interstitial scarlatinal nephritis of man is the same kind of reaction.

On the other hand, the killed culture or its product produced primarily lesions of the glomerular capillaries, in consequence of which the vascular loops became occluded with thrombi and later adherent to Bowman's capsule. Other glomerular tufts became enlarged through the appearance of numbers of endothelial cells in the lumina of the

15. Longcope, W. T.: J. Clin. Investigation **5**:7, 1927.

16. Duval, C. W., and Hibbard, R. J.: Proc. Soc. Exper. Biol. & Med. **24**: 876, 1927.

capillaries. The subcapsular spaces generally contained blood in the form of hyaline masses, also albuminous material and desquamated epithelium. Later, in those subcapsular spaces where hemorrhage had occurred, early proliferation (formation of "crescents") was noted. All these structural changes caused the glomeruli to undergo further and more serious alteration through replacement of the destroyed capillary loops by fibrous tissue.

While alterations in the tubular epithelium were not an early feature in either the glomerular or the interstitial type of experimental scarlatinal nephritis, the tubular epithelium was affected later in the process, degeneration appearing, especially in the epithelium of the convoluted portion of the tubule. Here the lining cells became swollen through the presence of fluid, granules, fat and hyaline droplets. Often the lumen was filled with blood, desquamated epithelium and granular and hyaline casts.

It seems likely that injuries to the glomeruli occasioned by the streptococcal toxic product account for most, if not all, of the urinary abnormalities, since albumin, bile, blood and the substances comprised in casts commonly appear in the urine simultaneously with structural changes that are confined to the renal tufts. The elimination of dye revealed the fact that the chlorides are normally filtered through the glomeruli and that the tubular epithelium has little or no excretory power for this salt. There was considerable evidence to show that the normal tubular epithelium is concerned mainly with the altering of the filtrate from the glomeruli through selective absorption by the lining cells. It is further to be remarked that the secretion of uric acid was not affected in these animals, though in all of them there was marked glomerulonephritis without structural changes in the tubules. Thus it would seem that the tubular epithelium, and not the tufts, have to do with the concentration of glomerular filtrate, selecting out and turning back into the circulation water, chlorides, etc., since they always appeared histologically normal when the glomeruli were badly injured.

Dogs with acute glomerulonephritis and no tubular changes excreted little urine as compared with the normal amount, indicating that the function of the tubular epithelium was unimpaired. Albumin and blood, undoubtedly have their origin in the glomerular tufts, as these substances occurred only when the capillaries were injured. Combined glomerular and tubular lesions did not quantitatively affect these abnormal substances in the urine. Albuminuria and hematuria always signified well defined alterations in the capillaries of the tufts, which was confirmed by histologic study. Casts were numerous and early in the streptococcal glomerulonephritis, because of the injured capillary tufts from which presumably these substances are derived, and by reason

of the fact that their formation is aided in the lumina of the tubules through the abstraction of water by the normal tubular epithelium.

Dogs in which there was induced an acute glomerular nephritis with the toxic product of scarlatinal streptococci returned, after a period of weeks, to a normal function, even though microscopic study of the sections of the kidney, still showed persistence of glomerular and tubular injuries, both acute and chronic. The ability of such animals to regain the normal function under these circumstances depended apparently not on regeneration, but on the fact that much of the renal parenchyma had escaped injury and was adequate for the carrying on of the renal function that is consistent with health. Dogs that were unable to effect a return to normal function after they had shown all the clinical evidence of acute glomerular nephritis and had finally succumbed may be regarded as suffering from a severe primary effect which involved too great a number of the glomeruli. These dogs showed the functional expression and structural changes incident to chronic diffuse nephritis.

CONCLUSIONS

In all essentials the renal lesions of experimental scarlatinal nephritis in the dog correspond to those of scarlatinal nephritis in man. In dogs the toxic product of S. scarlatinae has a selective action on the kidney resulting commonly in acute glomerulonephritis. This nephrotoxin primarily affects the endothelium of the glomerular blood vessels, causing in them an albuminous and fatty degeneration. The capillary endothelial lesions are frequently followed by hyaline thrombi and the rupture of the blood vessels with hemorrhage into the subcapsular space. Secondary changes of a retrograde character occur in the tubular epithelium, more especially in that of the convoluted portion.

The "killed" culture of scarlatinal streptococci acts in the same manner as the lysate in the production of experimental nephritis. A single large dose of this nephrotoxin often causes a fatal acute hemorrhagic glomerulonephritis. Furthermore, in dogs surviving the acute nephritis from a single dose chronic diffuse nephritis commonly develops weeks and months afterward. "Living" scarlatinal streptococci cause, in addition to glomerular lesions, an interstitial nephritis characterized by an intertubular lymphocytic infiltration.

The renal injury produced by one dose of scarlatinal nephrotoxin is always aggravated by a second injection. Such an exacerbation may be regarded as allergic, since the primary dose may have induced a hypersensitive state of the kidney. However, it is my belief that the lesions following the first dose are not allergic, but are caused by the destructive action of the streptococcal poison.

The urinary findings in acute nephritis in the dog are in general a fairly reliable index to the character and location of the renal lesions. Blood in the urine indicates hemorrhage into the subcapsular space. Hyaline casts are indicative of an impairment of glomerular function, which increases as the injury becomes intensified. Granular casts signify degeneration of the tubular epithelium. Albumin appears in the urine when there are degenerative changes of the glomeruli. Severe injury to the glomerular structures invariably causes a reduction in the amount of urine, while additional injury to the tubular epithelium does not further depress elimination.

The experimental nephritis produced in the dog with the toxic product of S. scarlatinae has afforded the opportunity to trace the progress and relationship of the various anatomic changes, and to correlate these with renal physiologic disturbances as expressed by abnormal substances in the urine.

ANOMALOUS ORIGIN AND COURSE OF THE LEFT CORONARY ARTERY*

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Anomalies of the origin and course of the coronary arteries are common, but the particular anomaly described here is so rare that reporting it seems justifiable.

A man, aged 65, came to the Mayo Clinic because of symptoms of urinary obstruction due to benign hypertrophy of the prostate gland. Prostatectomy was performed, and six days afterward the patient died. Death was due to embolic pneumonia and renal insufficiency.

Examination of the heart at necropsy disclosed only one coronary orifice. This was situated behind the right anterior aortic cusp, in the position normally occupied by the orifice of the right coronary artery. It was considerably larger than the normal coronary orifice, measuring 4.5 mm. in diameter, as against a normal orifice of 3 mm. This was found to be the common orifice for the two arteries, the larger of which curved toward the right, to enter and follow the right part of the coronary sulcus to the posterior surface of the heart. All branches of sufficient size to permit being opened or probed were traced carefully; the course and distribution appeared to be identical with that of the normal right coronary artery.

The smaller artery, which must be regarded as an anomalous left coronary artery, passed downward and to the left, at the root of the aorta and beneath the muscle of the posterior wall of the right ventricle. In this situation it was about 1 cm. below the valves of the pulmonary artery. It passed directly to the left, lost its relationship to the anterior wall of the aorta and took its course through the muscle of the right ventricle. On reaching the interventricular septum, it curved anteriorly in the right half of the septum, to reach the anterior surface of the heart. Three millimeters deep in the septum it gave off a branch, which passed downward through the muscle for a distance of 1 cm.; there it became superficial and continued its downward course to the apex.

Immediately after the main branch emerged from the interventricular septum, it divided into two branches, an ascending branch and a descending branch. The ascending branch, which was the larger, turned acutely upward and slightly to the right for a short distance. Continuing its upward course, it then curved slightly to the left to reach the left part of the coronary sulcus. From this point

* Submitted for publication, May 2, 1931.
* From the Section on Pathologic Anatomy, the Mayo Clinic.

it followed the course of the normal circumflex branch of the left coronary artery to the posterior surface of the left ventricle. The descending branch took its course downward and to the left, and gave rise to several smaller vessels. These small vessels definitely descended toward the apex. The two descending branches of the left main artery appeared to furnish the blood supply to most of the area which is normally supplied by the anterior descending branch of the left coronary artery (figs. 1 and 2).

Abbott,[1] in her extensive consideration of congenital cardiac disease, stated that both coronary arteries may arise behind a single aortic cusp, or that one coronary artery may be absent. However, she did not give definite details. Bochdalek[2] described a case in which there was one coronary orifice behind the right anterior cusp of the aorta, and from this there arose one abnormally large artery, which, after a short distance, divided into three branches; the first took the course that is normally taken by the right coronary artery; the second took the course of the circumflex branch of the normal left coronary artery, and the third passed to the left, through the muscle of the posterior wall of the right ventricle. It finally passed anteriorly, through the interventricular septum, to reach the surface of the heart, and turned downward, taking a course similar to that of the anterior descending branch of the left coronary artery.

Engelman[3] quoted Hyrtl, Thebesius, Otto and Cruveilhier, who had observed that the two coronary arteries may arise either from a common trunk or from one sinus of Valsalva. He recorded a case of his own in which there was only one coronary orifice; it was situated behind the left anterior aortic cusp, and from this, one large artery arose which soon divided into two branches. One branch passed to the left, as does the circumflex branch of the normal left coronary artery. The other branch passed downward for a distance of 0.5 cm., where a relatively small branch passed to the right between the roots of the aorta and pulmonary artery and continued its course in the right coronary sulcus to the posterior surface of the heart. Engelman considered this branch as the right coronary artery arising from a branch of the

1. Abbott, Maude E.: Congenital Cardiac Disease, in Osler, William; and McCrae, Thomas: Modern Medicine, ed. 3, Philadelphia, Lea & Febiger, 1927, vol. 4, p. 794.

2. Bochdalek: Anomaler Verlauf der Kranzarterien des Herzens, Virchows Arch. f. path. Anat. **41**:260, 1867.

3. Engelman, Guido: Ein Fall von mangeleiner Coronararterie, Anat. Anz. **14**:348, 1897-1898.

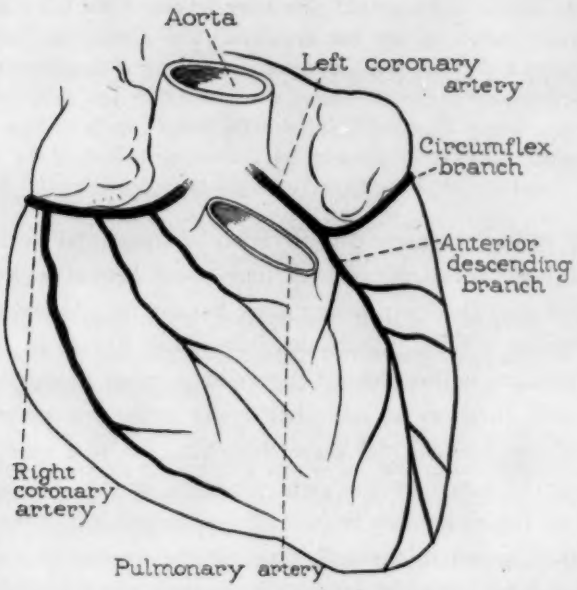

Fig. 1.—Anterior view: normal origins and courses of the coronary arteries.

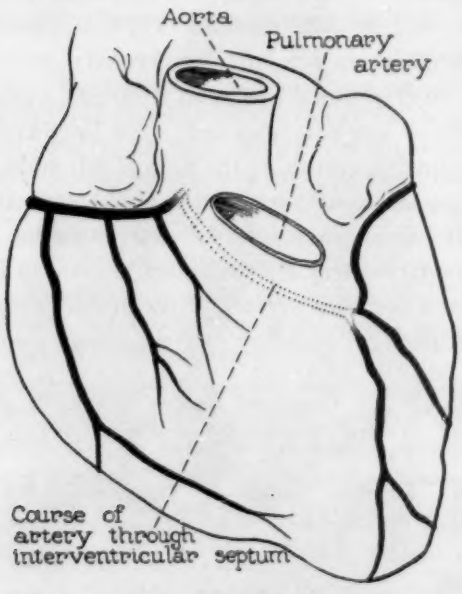

Fig. 2.—Origin and courses of coronary arteries described.

left coronary artery. The main descending branch continued its course downward for a distance of 0.5 cm., where it divided into two branches. The smaller of these branches took the course of the anterior descending branch of the normal left coronary artery. The larger branch, which he called an abnormal branch, passed downward and slightly to the right, over the anterior surface of the right ventricle, and continued over the right border of the heart to the posterior surface of the right ventricle.

Gallavardin and Ravault [4] reported a case apparently identical with the one that I have described.

Smith and Graber [5] reported the congenital absence of the left coronary artery. A small artery, coursing to the left, was given off by the main artery.

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4. Gallavardin, L., and Ravault, P.: Anomalie d'origine de la coronaire antérieure, Lyon méd. **136**:270, 1925.

5. Smith, F. M., and Graber, V. C.: Coronary Thrombosis with Congenital Absence of the Left Coronary Artery, Arch. Int. Med. **38**:222, 1926.

HOMOIOTRANSPLANTATION AND HETEROTRANSPLANTATION IN THE GUINEA-PIG

EFFECTS OF GRADED DEGREES OF HEAT ON CARTILAGE AND ON THYROID GLAND *

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In a series of papers Loeb has analyzed the factors that determine the reaction of the host against transplanted tissue.[1] These observations established the fact that there are characteristic qualitative and quantitative differences in the reaction of the host against homoiotransplanted, as compared with that against heterotransplanted, tissues. Loeb attributed these characteristic reactions of the host to substances given off by the transplanted tissues, and he designates these substances as homoiotoxins and heterotoxins, which differ from each other in the intensity and also in the character of the reactions which they call forth. There were strong indications that typical homoioreactions were elicited only by living tissue, whereas heteroreactions were called forth also by nonmetabolizing tissue, such as coagulated blood. It is of interest in this connection that Loeb and Drake found it possible to produce various grades of injury in amebocyte tissues by heating the tissues within a relatively small range of temperature and time of exposure, and by this means were able to reduce the activity of the cells to various stages intermediate between normal function and death.[2] Similarly in his earlier experiments, Loeb was able to reduce the growth energy of transplantable tumor tissue by subjecting the tissue to graded degrees of heat and also to the action of certain chemicals before transplantation.[3]

It was thought, then, to be of importance to determine if by reducing the activity of various normal tissues by exposing them to graded intensities of heat before homoiotransplantation, the reaction of the host would be decreased in proportion and whether any parallelism could be found between the reduction in growth activity of the transplant and the diminution in the intensity of the reaction of the host. In

* Submitted for publication, May 2, 1931.

* From the Department of Pathology, Washington University School of Medicine.

1. Loeb, Leo: Transplantation and Individuality, Physiol. Rev. **10**:547, 1930.

2. Loeb, Leo; and Drake, Dorothy: J. M. Research **44**:447, 1924.

3. Loeb, Leo: J. M. Research **8**:44, 1902; Virchows Arch. f. path. Anat. **172**: 345, 1903; Am. Med. **5**:412, 1903; **10**:265, 1905. Corson-White, E. P., and Loeb, Leo.: Centralbl. f. Bakt. **56**:488 and 325, 1910.

addition it was hoped that an answer would be found to the question whether any differences exist in these regards between the behavior of tissues that have a great potentiality to proliferate mitotically, such as those of the thyroid gland, and that of tissues that have less capacity to grow by mitotic division, such as cartilage; and, also it was hoped to study any differences that may exist in these respects between homoiotransplantation and heterotransplantation.

METHOD

For this purpose the thyroid glands and pieces of xiphoid cartilage of guinea-pigs and of rats were excised and pieces placed in test tubes containing sterile Ringer's solution. These test tubes were then immersed in a water bath of constant temperature, which had been previously heated to the desired temperature; the various temperatures used were 43, 45, 47, 49 and 51 C. Series of pieces of tissue were allowed to remain in the waterbath at each of these temperatures for fifteen, thirty and forty-five minutes, respectively. The pieces were then transplanted into subcutaneous pockets of guinea-pigs. In the case of heterotransplantation thyroid glands and cartilage of rats were transplanted into guinea-pigs. In every case the transplants were removed after twenty days, and sections were made for microscopic study.

HOMOIOTRANSPLANTATION OF THYROID GLAND

Heated at 43 C.—The recovered thyroid gland homoiotransplants that had been heated at 43 C. for fifteen, thirty and forty-five minutes, respectively, consisted in each case, chiefly of a central necrotic portion in which some colloid masses were seen, a few of which were lined by living acinar cells. This central necrotic portion was surrounded by fibrous tissue in which no remaining thyroid gland tissue was found. There were a number of clumps of lymphocytes and many scattered lymphocytes throughout the connective tissue. The surrounding transplanted fat tissue was fairly well preserved, but some scattered as well as massed lymphocytes and a small amount of connective tissue had invaded it. There were no essential differences between the transplants that had been heated for fifteen, thirty and forty-five minutes, respectively.

Heated at 45 C.—The homoiotransplants that had been heated at 45 C. for fifteen, thirty and forty-five minutes, respectively, consisted, in each case, chiefly of a small necrotic central portion, surrounded by a great mass of dense fibrous tissue through which there was scattered only a rather small number of lymphocytes. Connective tissue had penetrated into and replaced the greater part of the necrotic central portion of the transplanted tissue. There were a few remnants of thyroid gland acini, among which a few epithelial cells were still well preserved. However, no colloid was seen in any of the sections. The surrounding fat tissue was fairly well preserved, but many foreign body

giant cells were seen, replacing portions of fat tissue. No essential differences existed between the various specimens exposed for the different periods of time.

On the whole in these specimens, as compared with those that had been heated at 43 C., there was a rather definite decrease in the number of lymphocytes, with an increase in the amount of connective tissue. Giant cells were also more abundant in the fat tissue in this series than in the former one.

Heated at 47 C.—In the homoiotransplants that had been heated at 47 C. for fifteen, thirty and forty-five minutes, respectively, some differences in appearance were noted that accorded with the time of heating. In those that had been heated for fifteen minutes there was found chiefly a completely fibrosed mass of tissue, through which were scattered considerable numbers of single lymphocytes, as well as small masses of lymphocytes. The central necrotic mass, as well as the surrounding fat tissue, was almost entirely replaced by fibrous tissue. No thyroid gland tissue or colloid remained.

The transplants that had been heated for thirty minutes consisted chiefly of loose vascular connective tissue surrounding a central dense fibrous mass. Lymphocytes were scarce in these sections. The transplanted fat tissue was well preserved, and there was practically no reaction on the part of the connective tissue and lymphocytes, nor were there giant cells about it. No thyroid gland tissue remained.

The transplants that had been heated for forty-five minutes showed no trace of thyroid gland; lymphocytes were practically absent. However, there was a small amount of connective tissue present, and the transplant consisted chiefly of fat and rather loose connective tissue. The fat was being phagocytosed by large mononuclear cells.

Heated at 49 C.—The homoiotransplants that had been heated at 49 C. for fifteen minutes consisted chiefly of necrotic material and of fat tissue, which was being phagocytosed by large mononuclear cells, or of fibrous tissue that had replaced the necrotic tissue. There was only a slight connective tissue reaction. No thyroid gland tissue remained preserved. Lymphocytes were practically absent in the tissue. While those heated for fifteen minutes showed considerable necrosis and only a small amount of connective tissue, those heated for forty-five minutes showed no necrotic tissue and a large amount of connective tissue. In this case the connective tissue appeared to have entirely replaced the central necrotic mass that was noticeable in practically the whole former series.

Heated at 51 C.—The pieces of thyroid gland that had been heated at 51 C. for fifteen, thirty and forty-five minutes and then transplanted showed no essential difference from those that had been heated at 49 C.

Therefore, on the whole in this series, the lymphocytic reaction of the host in homoiotransplantation of thyroid gland varied inversely with the increased degree of heating, while the connective tissue reaction varied directly with the increased degree of heating; the greater the degree of heating the greater was the connective tissue reaction. However, since no thyroid gland remained preserved in the specimens heated to the higher degrees, it is not possible to ascertain whether the reaction noted occurred at a time when some tissue of the thyroid gland remained or whether it occurred subsequently to the destruction of the thyroid gland tissue. Additional experiments in which the time of examination is varied are necessary for the determination of this point.

HETEROTRANSPLANTATION OF THYROID GLAND

Heated at 43 C.—In the rat thyroid glands that had been heated at 43 C. for fifteen, thirty and forty-five minutes, respectively, and then transplanted to guinea-pigs there was found chiefly a very vascular connective tissue in which no remnants of preserved thyroid gland tissue were seen. Lymphocytes and polymorphonuclear leukocytes were abundant in all the sections, but the relative proportions of the lymphocytes and the polymorphonuclear leukocytes varied; in some specimens polymorphonuclear leukocytes predominated, while in others the lymphocytes were more numerous. The fat tissue was to a large extent replaced by connective tissue. Only occasional giant cells were seen.

Heated at 45 C.—The heterotransplants that had been heated to 45 C. for fifteen, thirty and forty-five minutes were found to be very similar to those described in the foregoing paragraph, except that the lymphocytes were perhaps somewhat less numerous in the series heated at 45 C., so that the polymorphonuclear leukocytes predominated in the majority of the sections.

Heated at 47 C.—In the heterotransplants heated at 47 C. for fifteen, thirty and forty-five minutes again no preserved thyroid gland tissue was found. They consisted in each case chiefly of a mass of vascular connective tissue in the center of which there was a small area of necrosis which contained varying numbers of polymorphonuclear leukocytes and necrotic débris. The lymphocytes were somewhat fewer and more scattered as compared with those in the transplants that had been heated at 45 C. The polymorphonuclear leukocytes were also somewhat decreased in number, but the connective tissue reaction was, on the whole, somewhat greater.

Heated at 49 and 51 C.—The heterotransplants that had been heated at 49 and 51 C. for fifteen, thirty and forty-five minutes consisted chiefly, in each case, of a mass of vascular connective tissue among the cells of which there were considerable numbers of scattered lymphocytes

and polymorphonuclear leukocytes. The fat tissue was invaded by large mononuclear phagocytic cells, fibroblasts and some polymorphonuclear leukocytes. Giant cells were scarce. No remnants of thyroid gland were seen.

On the whole, I found very noticeable differences between the reactions of the host to heterotransplants as compared with those to homoiotransplants, so far as in the former specimens polymorphonuclear leukocytes were found in great numbers, while in the latter specimens they were scarce or entirely absent. Furthermore, the heating of the heterotransplants was effective to only a slight degree in reducing the polymorphonuclear and lymphocytic reactions of the host, while the lymphocytic reaction of the host to homoiotransplants was reduced very markedly by the heating. In heterotransplantation as in homoiotransplantation the connective tissue reaction was greater in the specimens that had been heated at the higher degrees of temperature, as compared with those that had been heated at the lesser degrees.

HOMOIOTRANSPLANTATION OF CARTILAGE

Heated at 43 C.—The homoiotransplanted cartilage that had been heated at 43 C. for fifteen, thirty and forty-five minutes consisted of cartilage, perichondrium and the surrounding fat and connective tissue, all of which were in a fair state of preservation. Surrounding the transplant there was a marked lymphocytic and connective tissue reaction, which extended into the fat tissue and slightly into the cartilage, especially in areas in which some injury had occurred in the latter. There were also noted occasional giant cells in the surrounding fat tissue. On the whole, these transplants appeared similar to homoiotransplants of unheated cartilage removed at the same time.

Heated at 45 C.—In the homoiotransplanted cartilage and surrounding tissue that had been heated at 45 C. for fifteen minutes, the results were similar to those described in the foregoing paragraph: no effects of the heating were observable. On the other hand, the cartilage transplants that had been heated for thirty minutes showed what was interpreted as mild effects of the heating. The cartilage cells were no longer clearly discernible in the red-staining peripheral areas, although in the large majority of cases in the more central areas the transplanted cartilage cells were still fairly well preserved. There was a marked lymphocytic and connective tissue reaction, which in some cases extended into the cartilage.

The transplanted cartilage that had been heated for forty-five minutes was also in a fair state of preservation, although the zone of destroyed cartilage was somewhat greater here than in the cartilage that had been heated for only thirty minutes. As far as the number of lymphocytes

or the intensity of the connective tissue reaction was concerned there was no appreciable difference between these specimens and the previously described grafts.

Heated at 47 C.—Heating for fifteen minutes at 47 C. resulted in still greater injury to the cartilage cells, the cartilage now staining deeply with eosin throughout, instead of with hematoxylin in the central parts, as is usually the case in the areas where the cartilage is thicker. Cartilage cells were scarce, although the perichondrial cells appeared little altered. Lymphocytes were present, but in numbers definitely less than in those transplants that had been heated at 45 C. The connective tissue reaction showed no appreciable quantitative change. The transplanted connective tissue surrounding the cartilage was hyalinized and was in the process of replacement by newly formed connective tissue of the host. Those specimens that had been heated for thirty minutes generally showed the cartilage cells to be almost entirely destroyed, whereas the perichondrial cells remained well preserved and in the majority of cases displayed some proliferative activity. Hypertrophic spindle-shaped cells penetrated into the destroyed cartilage and formed new cartilage. In order to determine whether this regeneration of cartilage occurred specifically in those transplants that had been heated at 47 C. for thirty minutes, an additional series of experiments was carried out in which the cartilage was heated at 47 C. for fifteen, thirty and thirty-five minutes. Six pieces were heated for thirty-five minutes, six for fifteen minutes and twelve for thirty minutes. Seven of the twelve that had been heated for thirty minutes showed some regeneration of cartilage, whereas three of the six that had been heated for fifteen minutes showed it, and only one of the six that had been heated for thirty-five minutes showed it.

The lymphocytic reaction throughout this series was either entirely absent or present only as a few scattered cells in the surrounding fat and connective tissue. The connective tissue reaction was also diminished to some extent, although the greater part of the fat and connective tissue that surrounded the cartilage had been replaced by loose vascular connective tissue of the host.

It seems that in heating the cartilage for from fifteen minutes to thirty-five minutes at 47 C. before homoiotransplantation the cartilage was injured to such a degree that it became necrotic following transplantation, whereas the perichondrium evidently remained alive. Then, in accordance with the observations of Loeb,[4] the contact with the necrotic cartilage stimulated the perichondrial cells to proliferate to form new cartilage cells, which in some cases pushed their way into and replaced considerable amounts of the necrotic cartilage. It seems that this

4. Loeb, Leo: Am. J. Path. **2**:111 and 315, 1926.

regeneration of cartilage occurred at its optimum in the specimens that had been heated at 47 C. for thirty minutes.

In those heated at 47 C. for forty-five minutes, the entire transplanted tissue, including cartilage matrix, cartilage cells, perichondrium and the surrounding fat and connective tissue stained homogeneously with eosin. There were no preserved cells in the transplanted tissue. There was practically no connective tissue or lymphocytic reaction noticeable, and the transplant lay as an inert mass in the meshes of a network of loose edematous connective tissue.

Heated at 49 and at 51 C.—The homoiotransplants heated at 49 and at 51 C. for fifteen, thirty and forty-five minutes showed essentially the same picture as those that had been heated at 47 C. for forty-five minutes. Occasionally a few lymphocytes were seen, and occasionally the connective tissue was somewhat dense, instead of loose and edematous. Phagocytic cells and foreign body giant cells penetrated in rather large numbers into the peripheral portions of the transplanted tissue.

HETEROTRANSPLANTATION OF CARTILAGE

Heated at 43 C.—The heterotransplants of cartilage that had been heated at 43 C. for fifteen, thirty and forty-five minutes consisted in each case of a necrotic mass of cartilage surrounded by masses of lymphocytes and polymorphonuclear leukocytes and connective tissue. No cartilage cells remained. The cells of the perichondrium in a few cases, however, appeared fairly well preserved. There was no regeneration of cartilage.

Heated at 45 C.—The heterotransplants that had been heated at 45 C. for fifteen, thirty and forty-five minutes showed no preserved cartilage cells; the cells of the perichondrium were also destroyed. There were considerable numbers of scattered lymphocytes, and a few clumps of these cells and some polymorphonuclear leukocytes were present. Both of these elements were perhaps somewhat decreased as compared with the transplants that had been heated at 43 C. On the other hand, the connective tissue reaction was possibly somewhat greater here than in the former series.

Heated at 47 C.—The heterotransplants that had been heated at 47 C. for fifteen, thirty and forty-five minutes presented a picture very similar to that seen in the heterotransplants that had been heated at 45 C. The cartilage and the surrounding fat and connective tissue were entirely necrotic, and there were considerable numbers of lymphocytes and occasional polymorphonuclear leukocytes in the surrounding tissues. There was little penetration of these cells into the cartilage. The connective tissue reaction appeared to be slightly stronger in these than in the transplants heated at 43 and at 45 C.

Heated at 49 and at 51 C.—Pieces of cartilage heated at 49 and at 51 C. for fifteen, thirty and forty-five minutes appeared very similar to those heated at 47 C. Each consisted of necrotic cartilage which lay in the center of a network of edematous hyaline fibrous tissue through which were scattered considerable numbers of lymphocytes and polymorphonuclear leukocytes. Occasional giant cells were seen in the tissues that surrounded the transplant.

CONCLUSIONS

Heating thyroid gland at degrees of heat ranging from 43 to 51 C. preceding homoiotransplantation causes a marked lessening of the lymphocytic reaction of the host ordinarily occurring after homoiotransplantation. The connective tissue reaction, however, appears to be somewhat increased with the heating to the higher degrees.

Heating thyroid gland at graded degrees preceding heterotransplantation is only slightly effective in diminishing the reaction of polymorphonuclear leukocytes and lymphocytes of the host ordinarily occurring after heterotransplantation. The connective tissue reaction also appears to be somewhat greater here than that ordinarily occurring after heterotransplantation of unheated thyroid gland.

Exposing cartilage to graded degrees of heat preceding homoiotransplantation causes a marked and graded decrease in the lymphocytic reaction as well as in the connective tissue reaction of the host ordinarily occurring after homoiotransplantation of cartilage. This reduction in the reaction of the host is concomitant with a marked increase in the growth activity of the transplanted cartilage, as manifested by hypertrophy and hyperplasia of the perichondrial cells, which proliferate and lay down new cartilaginous matrix. This regeneration of cartilage occurs at its optimum in transplants of cartilage that have been heated at 47 C. for thirty minutes before transplantation.

Heating cartilage at graded degrees of heat preceding heterotransplantation is only slightly effective in causing a reduction in the polymorphonuclear leukocytic and lymphocytic reactions of the host ordinarily occurring after heterotransplantation. The connective tissue reaction on the part of the host against the transplanted tissue appears to be somewhat increased in amount over that which occurs ordinarily against unheated cartilage.

Homoiotransplants killed before transplantation by mild degrees of heat no longer elicit a homoioreaction, while heterotransplanted tissue, under the same conditions, still calls forth a definite heteroreaction on the part of the host.

Laboratory Methods and Technical Notes

METHOD FOR EXAMINING THE APPENDIX*

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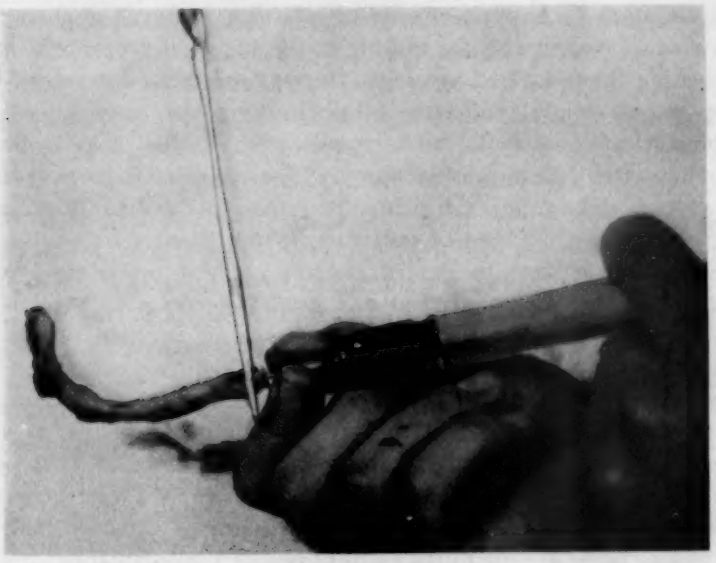
DEMONSTRATION OF A PERFORATION OF THE APPENDIX

Perforations in gangrenous appendixes are not as easily demonstrable as is believed. In my experience, gangrenous appendixes that presumably should be perforated were not, and vice versa. Even the histologic picture is frequently deceptive. What appears to be a frank necrosis



A method of demonstrating the presence and location of a perforation in an appendix.

involving all the coats of a part of an appendix fails to reveal a perforation. The method suggested allows the determination of a perforation and the localization of the lesion.

An ordinary 5 or 10 cc. syringe is partly filled with a weak solution of eosin. A needle is attached to the syringe, and the needle is introduced into the lumen of the appendix through its proximal end. A hemostat is applied over the appendix and needle to keep the needle in place and to prevent the escape of the eosin (fig.). The hemostat is applied over that part of the appendix which shows the hemostat markings made by the surgeon. The piston of the syringe is gently pushed down so that the eosin solution runs into the appendical lumen. At the point of perfora-

* Submitted for publication, June 29, 1931.

* From the Laboratories and Department of Medical Research, Toledo Hospital.

tion, the eosin escapes through the wall and marks the point of the perforation. This method of filling the appendix was found preferable to the introduction of the fluid by gravity. The slight pressure exerted was not found to produce artificial perforations in gangrenous appendixes. If a permanent record is desired of the perforation and its location, iodized poppy seed oil 40 per cent may be introduced instead of eosin and a roentgenogram taken.

A METHOD OF CUTTING AND SECTIONING THE APPENDIX

The method that is commonly employed in cutting appendixes for gross and histologic study consists in making several transverse sections across the length of the organ. Such a method allows only an inspection of isolated parts and destroys relationships. If ten sections are made, the chance of locating a lesion histologically is 1 : 100,000 in an appendix 6 cm. in length and with sections 6 microns in width. The following method permits gross inspection of the lumen and of the wall of the entire organ and preserves the relationship of lesions to normal areas.

After the appendix is received from the operation room, it is placed in a 10 per cent formaldehyde solution for from six to twenty-four hours. The organ is then removed from the fixative and cut longitudinally with a long and flat-bladed knife. The cut is begun at the tip of the appendix with the heel of the knife and carried longitudinally through the approximate middle of the organ. The appendix is supported gently with the left hand, and the knife is carried in a single cut to avoid an irregular surface. At the completion of the section, two equal halves are obtained. Each half of the organ shows the lumen, its contents and the wall.

For histologic sections one or both halves may be used. Any method of handling the tissue preparatory to embedding may be employed. However, in my experience, it is preferable to use alcohol for dehydration and chloroform for clearing. Either celloidin or Warthin's celloidin sheet method or paraffin embedding may be selected. The paraffin method requires more skill and care in preventing wrinkles and tears. Sections 6 microns in width are made through various levels in which the appendical lumen persists. From five to ten sections will give a composite picture of the entire organ. The sections allow the determination of the width of the lumen and the relation of the opposing surfaces, and make it possible to study the whole length of the appendix in a single or two sections.

THE USE OF BUTYL ALCOHOL IN THE PREPARATION OF PARAFFIN SECTIONS*

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Tissue properly fixed in 10 per cent formaldehyde (any other fixative may be used) is rinsed in tap water to remove excess formaldehyde and then treated by immersion in 50 per cent alcohol (ethyl or methyl) for two hours, then in 80 per cent alcohol (ethyl or methyl) for two hours and then in 95 per cent alcohol (ethyl or methyl) for two hours or over night.

* Submitted for publication, May 29, 1931.

* From the Department of Pathology, University of California Medical School.

From 95 per cent alcohol the tissues are put directly into butyl alcohol (azo or normal), two changes covering a period of six hours, or the tissues may be left in the butyl alcohol over night without harmful results. From butyl alcohol the tissues are placed directly in paraffin (melting point from 56 to 58 C.), about three changes covering a period of twenty-four hours. They are then embedded. If one desires to put sections through more rapidly, as is required with surgical specimens, the same procedure can be followed by keeping all solutions in the oven at from 56 to 58 C. Sections can be completed in thirty-six hours.

The advantages of butyl alcohol are as follows: There is little of the shrinkage of tissue that occurs with absolute alcohol and xylene. Tissue can be left in butyl alcohol for from a day to a week, without harmful results. Large sections can be cut and ribboned with ease. The elimination of absolute alcohol and xylene means a tremendous saving in expense, for there is little evaporation of butyl alcohol, and a gallon, costing approximately $3.50, will do the same amount of work as 4 gallons of xylene and 5 gallons of absolute alcohol, costing approximately $30.

General Review

THE ETIOLOGY OF POSTVACCINIAL ENCEPHALOMYELITIS *

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SYNOPSIS

Clinical Picture
Epidemiology
- Period of Incubation
- Incidence in Relation to Number of Vaccinations
- Grouping of Cases
- Rural Distribution
- Incidence Considered in Relation to Strain of Virus Used, and in Relation to Reaction at Site of Vaccination
- Incidence in Relation to that of Other Nervous Diseases
- Incidence in Relation to Age

Morbid Anatomy
Possibly Related Conditions
- Encephalomyelitis Complicating Smallpox
- Encephalomyelitis Complicating Measles
- Nervous Complications of Varicella
- Nervous Complications of Mumps
- Other Postinfection Encephalitides
- Paralysis Complicating Antirabic Treatment
- Independent Conditions

Theories Regarding the Etiology of Postvaccinial Encephalitis
- Accidental Relationship
- Vaccinia Virus as the Direct Cause
- Activation of Some Other Virus
- Allergy

Prophylaxis and Treatment
Summary

The occurrence, in recent years, of a serious acute disease of the central nervous system complicating the oldest and as yet the most effective of the procedures for immunization has attracted widespread concern. Although general attention was first called to the possibility that such a complication occurs by the report of Lucksch in 1924,[1]

* Submitted for publication, Feb. 7, 1931.

* From the Department of Bacteriology, College of Physicians and Surgeons, Columbia University.

1. Lucksch, Franz: Med. Klin. **20**:1170, 1924.

it was apparently first recognized in 1922 in England when four patients with an acute fatal nervous condition and a history of recent vaccination were admitted to the London Hospital. The essential lesions, as found at autopsy, were those of an acute diffuse nonpurulent encephalomyelitis. Further inquiry revealed seven similar cases in the London area. Turnbull and McIntosh, in 1926,[2] reported these cases with full pathologic observations, and included the reexamination of a similar case that occurred in 1912. During the summer of 1923, fifty-one other cases were reported in various districts throughout England, and in November of that year the Andrewes committee was appointed by the Minister of Health to investigate the condition.[3]

In Bohemia, in 1923, Lucksch [4] performed autopsies in three cases of nervous disease closely following vaccination, and at first considered the pathologic changes to be those of epidemic encephalitis. In Holland, in 1924 and 1925, reports of thirty-five cases were collected by Bastiaanse,[5] and sporadic cases were reported from various other countries in Europe (Stiner,[6] Hauswirth,[7] Frommel and Baumgartener,[8] Jehle,[9] Report of League of Nations Commission on Vaccination [10]).

Since these earlier reports, a considerable number of cases have occurred in various parts of the world, and attempts have been made to reconstruct from records cases that occurred before such a possibility was recognized. Holland and England have had by far the greater number of cases; only in these countries and possibly in Germany has the condition approached epidemic proportions. Jitta [11] gave a total of 197 cases reported in Holland to and including 1928, with the peak of the incidence curve lying between 1924 and 1927. A considerable number of cases was still being reported to September, 1929,[12] making a total of well over 150 definite cases to that time. In the combined Andrewes-Rolleston reports [3] on the disease in England, 93 definite cases were reported to and including 1927, most of them occurring in

2. Turnbull, H. M., and McIntosh, James: Brit. J. Exper. Path. **7**:181, 1926.

3. Report of Ministry of Health Committee on Vaccination, London, His Majesty's Stationery Office, 1928.

4. Lucksch, Franz: Centralbl. f. Bakteriol. (Abt. 1) **96**:309, 1925.

5. Bastiaanse, F. S. van B.: Bull. Acad. de méd., Paris **94**:815, 1925.

6. Stiner, O.: Schweiz. med. Wchnschr. **6**:244, 1925.

7. Hauswirth, A.: Schweiz. med. Wchnschr. **7**:1113, 1926.

8. Frommel, E., and Baumgartener, J.: Schweiz. med. Wchnschr. **7**:857, 1926.

9. Jehle, quoted by Lucksch: Centralbl. f. Bakteriol. (Abt. 1) **103**:227, 1927.

10. Report of League of Nations Commission on Vaccination, 1928, League Publications, CH, 739.

11. Jitta, N. M. J.: Bull. de l'Office internat. d'hyg. pub. **22**:51, 1930.

12. Editorial, Lancet **2**:1154, 1929.

1923. Sporadic reports subsequent to that time brought the number to over 100 at the end of 1929. Germany had a total of approximately 40 cases from 1921 to 1930, with the majority in the period from 1927 to 1929.[13] Three cases were reported by Duken[14] and Widowitz[15] as late as June, 1930. Sweden to 1929 had had a total of about 25 cases, with 9 occurring in 1928.[16] Vienna and lower Austria contributed 28 cases from 1925 to 1929, 11 in 1929 (Knöpfelmacher,[17] Zappert[18]). In other countries in which the disease has occurred, there have been chiefly isolated and sporadic cases: France, 9;[19] Poland, 2;[20] Norway, 11;[21] Italy, 26; Japan and Argentina;[22] British Guinea.[23]

Since the recognition of the condition in Europe a number of cases of nervous complications following vaccination have been reported in this country; some of these clinically and pathologically conform to the typical European cases. Wilson and Ford,[24] in 1927, reported four cases from the records, the first of which occurred in 1922. In two of these cases, pathologic examination revealed lesions identical with the typical picture to be described in later paragraphs. Fulgham and Beykirch[25] and Tuthill[26] reported cases with a similar picture. Clinical cases resulting in recovery, or without satisfactory pathologic descriptions, have been reported by Graubarth,[27] Wolf and Brams[28] and Perritt and Carrell.[29] According to Armstrong,[30] possible cases,

13. Hamel: Bull. de l'Office internat. d'hyg. pub. **21**:2052, 1929.
14. Duken, J.: Ztschr. f. Kinderh. **50**:292, 1930.
15. Widowitz, Paul: Arch. f. Kinderh. **92**:81, 1930.
16. Kling, C.; Lonberg, N., and Wassen, E.: Bull. de l'Office internat. d'hyg. pub. **21**:2055, 1929.
17. Knöpfelmacher, W.: Wien. klin. Wchnschr. **43**:97, 1930.
18. Zappert, J.: Wien. med. Wchnschr. **80**:127, 1930.
19. Pagniez, P.: Presse méd. **38**:134, 1930.
20. Milukowski, V.: Schweiz. med. Wchnschr. **58**:506, 1928.
21. Ustvedt, Y.: Norsk. mag. f. laegevidensk. **91**:417, 1930; abstr., J. A. M. A. **95**:84, 1930.
22. Doerr, R., and Breger, E, in Kolle; Krause, and Uhlenhuth: Handbuch der pathogenen Microorganismen, Jena, Gustav Fischer, 1930, vol. 8, p. 1531.
23. Grace, A. W.: Tr. Roy. Soc. Trop. Med. & Hyg. **40**:337, 1930.
24. Wilson, R. E., and Ford, F. R.: Bull. Johns Hopkins Hosp. **40**:337, 1927.
25. Fulgham, J. H., and Beykirch, J. G.: J. A. M. A. **92**:1427, 1929.
26. Tuthill, Ruth: Arch. Neurol. & Psychiat. **24**:759, 1930.
27. Graubarth, Julian: Arch. Pediat. **46**:701, 1929.
28. Wolf, Henry; and Brams, W. A.: J. Nerv. & Ment. Dis. **71**:714, 1930.
29. Perritt, R. A., and Carrell, R. C.: J. A. M. A. **94**:793, 1930.
30. Armstrong, Charles: Pub. Health Rep. **44**:2041, 1929.

based on clinical and epidemiologic grounds, have been noted in eight states. No cases have as yet been reported in Canada.[31]

A number of attempts have been made to show the presence of this complication of vaccination previous to the recent recognized outbreaks. Comby [32] and Knöpfelmacher [33] recalled similar cases seen 20 years ago. Doerr and Breger [22] referred to Freund as having mentioned the possibility of this complication in 1897. Jorge [34] recalled two cases diagnosed as tuberculous meningitis reported by Carrier, and thinks it probable that accidents of this character have been happening for many years. According to Turnbull,[35] Sacco, 100 years ago, referred to nervous accidents consequent on vaccination. The Royal Commission on Vaccination of the years from 1880 to 1896 made no allusion to cerebral complications.[3] It seems possible, however, that occasional cases have occurred since the introduction of vaccination.

In any consideration of the etiology of these reported postvaccinial complications involving the central nervous system, the first explanation that presents itself is that these cases are merely coincidental nervous diseases that have no connection with vaccination. In view of the enormous numbers of vaccinations performed annually and the comparatively few cases reported, this explanation might appear to be correct. Preparatory to a discussion of the evidence against this chance relationship and of the other theories regarding the etiology, a review of the clinical picture, epidemiology and morbid anatomy of the complications will first be given. A group of possibly related conditions, knowledge of which is essential in a discussion of the etiology of postvaccinial encephalomyelitis, will be briefly reviewed.

CLINICAL PICTURE

In reviewing the first large group of English cases, the Andrewes committee [3] considered forty-seven of the sixty-two cases sufficiently similar clinically to be regarded as a "homogeneous" group. The picture in this group they described as follows: "In most instances the onset of symptoms was rapid and the course of the disease acute. The predominant symptoms were of cerebral rather than spinal origin and included fever, headache, vomiting, strabismus and varying degrees of clouding of consciousness. Where paralysis of the limbs occurred, it was generally of the upper motor neurone type." They regarded the symptomatology as indicating a diffuse inflammation of the brain without special localization and with little evidence of involvement of the spinal cord. The Rolleston committee [3] considered a total of forty more cases, twenty-five of which belonged in a homogeneous group presenting clinical features similar to those

31. Defries, R. D., and McKinnon, N. E.: Canad. M. A. J. **21**:516, 1929.
32. Comby, J.: Arch. de méd. d'enf. **10**:598, 1907.
33. Knöpfelmacher: Wien. klin. Wchnschr. **43**:97, 1930.
34. Jorge, R.: Bull. de l'Office internat. d'hyg. pub. **19**:37, 1927.
35. Turnbull, H. M.: Lancet **2**:43, 1929.

described by the Andrewes committee. In the later report it was emphasized that the cardinal symptoms—headache, vomiting, drowsiness and pyrexia—are constantly present in severe, and rarely absent in, mild cases. They may be the only symptoms present even in fatal cases.

The continental cases seem to have been somewhat more variable in their clinical aspects. Lucksch [36] classified the cases according to the clinically apparent localization of the lesions. In his first group, the symptoms pointed to an involvement of the meninges alone, with headache, vomiting, fever, opisthotonos, convulsions and increased pressure of the cerebrospinal fluid. In the second group, the brain itself was involved, as well as the meninges, with paresis and somnolence as additional symptoms. The majority of the Dutch cases fell into this group. Tetanus-like symptoms were imposed in some and were present in Lucksch's original cases and in some of the English cases. Knöpfelmacher [17] suggested that many cases of so-called tetanus following vaccination may in reality have been encephalitis. In another small group of cases, the muscles of the eye were affected with squinting and abducens paralysis, and in others disturbances of the bladder and rectum pointed to involvement of the cord, as well as of the brain. Knöpfelmacher,[17] concurring in Lucksch's classification, would have added to the cerebral group cases of epilepsy occurring after vaccination. Lucksch's third main group is composed of cases in which the symptoms were confined to the cord, giving poliomyelitis-like pictures, but without the residual disabilities. Knöpfelmacher would have added a fourth large group in which neuritis followed vaccination and quoted Zappert and Leiner and others as having observed cases of this type.

Excluding the few neuritides, poliomyelitis-like cases and epilepsies, the cases as a whole show a considerable degree of similarity and are generally accepted as representing a definite clinical entity, although, as Lucksch emphasized, the diagnosis cannot, with certainty, be made on a clinical basis alone.

The typical condition can be differentiated clinically from epidemic encephalitis by the presence of a positive Babinski sign, the lack of residual lesions or recessions and, in most cases, by the absence of involvement of the muscles of the eyes. From poliomyelitis, it is differentiated by the gradual onset of the paralysis, when it occurs, and by the usually complete recovery.[36]

The mortality in the English cases was 58 per cent; [3] in the Dutch cases it was about 35 per cent.[37] Flexner [38] thought that the difference in mortality is accounted for by the inclusion of more mild cases in the Dutch collections than in the English. In most of the English cases in which the patients survived, recovery was complete; some evidence of mental change was present in five of the twelve cases followed for a long period. Mental deterioration or residual paralysis occurred in a small proportion of the continental cases.

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36. Lucksch, Franz: Centralbl. f. Bakteriol. (Abt. 1) **103**:227, 1927.
37. Terburgh, J. T.: Nederl. tijdschr. v. geneesk. **71**:2, 18 and 10, 1927.
38. Flexner, Simon: J. A. M. A. **94**:305, 1930.

EPIDEMIOLOGY

Period of Incubation.—The time of onset of the nervous symptoms following vaccination has been carefully observed in a considerable number of cases. Chart 1, showing for each day after vaccination the number of cases having their onset on that day, is based on a total of 298 cases: 87 from the reports of the English committees, 123 from Terburgh's [39] report on the Dutch cases, 89 from Eckstein's [40] report on the disease in Germany and the remainder from isolated reports, including some of the cases in this country, in which a definite period of incubation was given. By far the great majority of cases (65 per cent) had their onset between the tenth and thirteenth days, and 82 per cent between the seventh and fourteenth days. The earliest day after vaccination on which an onset occurred was the second day. There

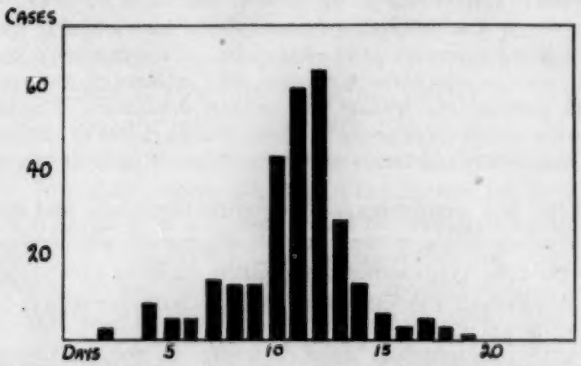

Chart 1.—Cases of postvaccinial encephalitis according to days of onset following vaccination. Twenty-one cases occurring between the twentieth and the thirty-fifth day are not shown on the chart.

is a sharp decline in the number of onsets after the thirteenth day, and only isolated cases began after the sixteenth day. The English commission found that the cases having their onsets very early or very late after vaccination were those occurring in infants. The German cases [40] taken alone show a greater distribution over the time chart and a much greater proportion occurring before the tenth day than is found in the total collection of cases. Chart 1 indicates a definite regularity in the time of occurrence of the disease after vaccination and justifies Keller [41] in speaking of a "normal" period of incubation.

Incidence in Relation to Number of Vaccinations.—Whether there is a definite relationship of the incidence of postvaccinial encephalitis

39. Terburgh, J. T.: Versl. med. Volksgezdh., 1929, p. 1302.
40. Eckstein, A.: Klin. Wchnschr. **8**:1153, 1929.
41. Keller, W.: Monatschr. f. Kinderh. **44**:222, 1929.

to the number of vaccinations performed is less certain. This proportional incidence has varied considerably in the various countries in which the disease has occurred. Possibly the highest incidence was that on the island of Marken,[42] where three of thirty-six vaccinated persons contracted encephalitis. The accompanying table indicates the great variability of the incidence expressed in number of vaccinations giving rise to one case.

Within the countries concerned, a somewhat closer relationship is shown, although discrepancies exist. The Andrewes Committee [3] made a careful study of the incidence in 1922 and 1923, in relation to the number of tubes of vaccine lymph issued each week during this period. Chart 2 is adopted from their report. The black columns in the upper part of the chart represent the postvaccinial cases of encephalitis accord-

TABLE 1.—*Incidence of Encephalitis Following Vaccination*

Place*	Author	Incidence in Relation to Number of Vaccinations
Island of Marken	Aldershoff	1 in 12
Holland, 1924-1927	Jitta	1 in 6,938
Holland, 1927	Jitta	1 in 3,074
Holland, 1928	Jitta	1 in 4,545
Sweden, 1924-1928	Kling, Lonberg and Wassen.	1 in 21,275
England	Bedson	1 in 48,823
Germany	Doerr and Breger	1 in 100,000
Switzerland	Sobernheim	1 in 333,000

* In the area of Paris in six years there have been 1,324,082 vaccinations with no cases (Bull. de l'Office internat. d'hyg. pub. **21**: 1133, 1929), and in Soviet Russia where there are from 8,000,000 to 9,000,000 vaccinations a year, no case of encephalomyelitis has yet been reported.

ing to the weeks in which the patients were vaccinated; those in the lower part, the tubes of lymph issued each week. The committee's conclusion that "there is undoubtedly an association in time between cases and the prevalence of vaccination throughout the country" seems justified by the chart. The relationship, however, is not a direct one, since a considerably smaller number of vaccinations performed in the summer of 1923 were followed by more cases than the greater number of vaccinations in 1922. The mortality in the cases in 1923 is not sufficiently lower to ascribe this difference in number to a greater recognition of milder cases as a result of more widespread knowledge of the condition.

In the different districts within England the relationship is not direct. The committee found that increased vaccination was accompanied by encephalitis in twenty-seven localities, but that in seven

42. Aldershoff, H., quoted by Doerr and Breger (footnote 22).

places encephalitis occurred without any increase in vaccination, and that in eighteen places increased vaccination did not result in any cases of encephalitis.

In other countries a more or less regular relationship between number of cases and number of vaccinations has been established. Hamel [13] and Eckstein [40] found that in Germany most of the cases occurred in May and June, the months when the most vaccinations were performed. In Holland from January to June, 1929, few vaccinations were performed, and only 5 cases of encephalitis were reported, but following this period, owing to an epidemic of smallpox, vaccinations were done in great numbers, and 68 cases resulted.[43] Terburgh [39] showed that over a period of three years in Holland 188,000 vaccinations were performed in March, with 46 cases; 99,000 in April, with

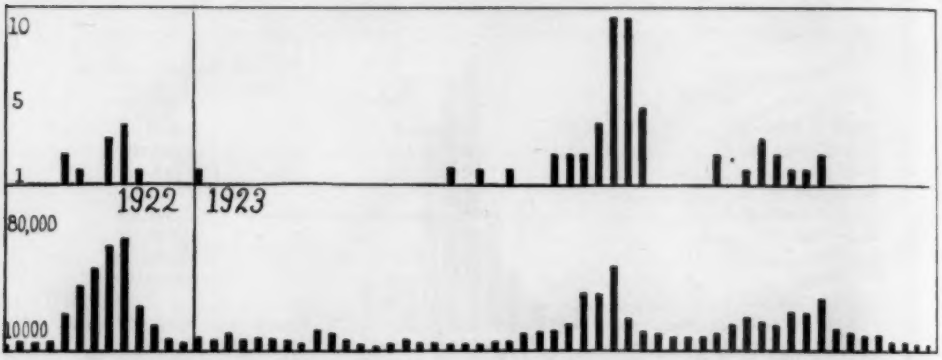

Chart 2.—Above: Cases of postvaccinial encephalitis in England from October, 1922, to December, 1923, according to the weeks when the patients were vaccinated. Below: Tubes of lymph issued each week during the same period. The chart is adopted from the Report of the Andrewes and Rolleston Committees on Vaccination, of the Ministry of Health, London, published by His Majesty's Stationery Office in 1928.

14 cases, and 46,000 in May, with 2 cases, indicating a rough proportionality of cases to vaccinations. As shown in the table, in Holland the incidence with relation to vaccinations varied from 1 in 6,938 from 1924 to 1927, to 1 in 3,074 in 1927. It may be concluded that a definite relationship exists between the number of vaccinations and the number of cases of encephalitis, but that this relationship is by no means directly proportional, and that within certain districts it is not evident.

Grouping of Cases.—Closely related to the lack of a directly proportional relationship between the cases of postvaccinial encephalitis and

43. Jitta, N. M. J.: Bull. de l'Office internat. d'hyg. pub. **21**:1886, 1929.

vaccinations is the so-called "group arrangement" of cases which has been noticed in many outbreaks of the disease. The English committees noticed that while many cases of the disease were isolated and sporadic, there was a tendency for groups of cases to occur closely associated in time and place, but with no evidence of a spread of infection, since the cases occurred almost simultaneously. They described the bulk of cases in July, 1923, especially, as "a simultaneous series of explosions apparently unconnected." The groups of cases were never very large—one of five cases was the largest—but they were conspicuous in contrast with the absence of cases elsewhere. The second report on the twenty-five cases in 1926 and 1927 also showed the occurrence of two definite groups of five and six cases. In Holland, nineteen of the first thirty-five cases occurred in groups of two or more in small communities. Doerr and Breger [22] emphasized the "high proportion of cases in a certain place at a certain time while the neighboring regions remained free." Gildemeister [44] mentioned three such outbreaks in Holland. Especially illustrative of this characteristic grouping were the eleven cases in the Kufstein region of the Tyrol [45] and the cases on the Island of Marken reported by Aldershoff.[42]

Grouping of cases of postvaccinial encephalitis in the same household or family has occurred, but comparatively rarely. The English committee reported two such instances, in each of which members of the family were vaccinated on the same day and showed symptoms on the same day. Two instances of more than one case occurring in the same family, but with two and three years intervening, are on record,[44] suggesting a peculiar familial susceptibility.

RURAL DISTRIBUTION

With the exception of the first cases in London in 1922, the English cases had a distinctly rural distribution; the explosive outbreaks occurred almost entirely in rural communities. The Rolleston committee [8] regarded a distribution among small hamlets and the very occasional incidence of familial cases as characteristic of postvaccinial encephalitis as of poliomyelitis and epidemic encephalitis.

The primarily rural distribution of the disease in Holland in the earlier cases, at least, is evident from figures calculated from the report of the Commission of Vaccinations of the League of Nations. From 1924 to 1927, the incidence per million of inhabitants in the communes, according to population was as follows: over 100,000, 13.5; from 20,000 to 100,000, 12.1; from 5,000 to 20,000, 14.7; under 5,000, 33.1. It seems likely, however, that more recently the rural predominance has decreased, for Jitta, in 1930,[11] stated that there is slight difference between the urban and rural incidence.

The rural distribution has not been evident in Germany. Eckstein [40] stated that there had been a slight preponderance of cases in the larger cities.

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44. Gildemeister, E.: Centralbl. f. Bakteriol. (Abt. 1) **110** (supp.) : 121, 1929.
45. Kaiser, M., and Liedl, E.: Ztschr. f. Desinfekt. u. Gesundhw. **21**:261, 1929.

Incidence Considered in Relation to Strain of Virus Used, and in Relation to Reaction at Site of Vaccination.—The occurrence of postvaccinial encephalitis in isolated small outbreaks suggests that certain strains or lots of virus may be responsible, but there is no evidence incriminating any strain or lot. Most of the English cases followed use of the government lymph, but the tubes involved were from many different series, and cases also followed the use of lymph from commercial sources in England and on the continent. In Holland lymphs from many sources have been used, and no one source has proved to be more associated with the occurrence of the disease than another.[10] It is generally accepted that the intensity or character of the reaction at the site of vaccination bears no relation to the occurrence of the disease, the reaction running a normal course in the great majority of the cases.

Incidence in Relation to That of Other Nervous Diseases.—The possible relationship of the incidence of postvaccinial encephalitis to the incidence of other epidemic nervous diseases is of some importance in determining the causal factor. The similarity in epidemiology between postvaccinial encephalitis, poliomyelitis and epidemic encephalitis has been referred to. The English committee found no association of the postvaccinial disease with epidemic encephalitis, but noted an association with poliomyelitis in 1923. The majority of the postvaccinial cases occurred just previous to the seasonal rise in poliomyelitis or in the autumn when poliomyelitis was still prevalent. The cases in 1922 occurred when the incidence of poliomyelitis was still greater than normal. The same relationship was not evident in 1926 and 1927, and a study of the largest group at this time showed no unusual incidence at the time of, or in the same place with, any other nervous disease. In Holland the early cases accompanied a rise in the number of cases of epidemic encephalitis, but later the number of the latter declined, while the number of postvaccinial cases increased.[22] There was no relation between the incidence of postvaccinial cases and that of poliomyelitis in Holland. In Bohemia, Lucksch [4] was unable to find any relationship between the occurrence of his cases and the occurrence of poliomyelitis or of encephalitis. In Germany, according to Doerr and Breger,[22] epidemic encephalitis had declined before postvaccinial encephalitis occurred. They pointed out that in France and the United States epidemic encephalitis is common, while postvaccinial encephalitis is rare. It is questionable whether any importance is to be attached to the apparent relationships to poliomyelitis in England and epidemic encephalitis in Holland. The apparent general increase in other postinfection and independent encephalitides coincidental with an increase in postvaccinial encephalitis, will be discussed in another section.

Incidence in Relation to Age.—The determination of a predilection in postvaccinial encephalitis for any special age is complicated by the differences in the laws regulating vaccination in the various countries. The frequencies according to age must be expressed in relation to the number of vaccinations in any one age group. However, from the various reports, it seems definite that infants have a relative insusceptibility to the disease. In England,[9] where 63.3 per cent of the vaccinations are performed on children under 1 year of age, it was shown that of ninety-three cases, fifty-nine should have been in children under 1 year of age, but that only nine of the cases were. The occurrence of cases in England was associated with an increased proportion of vaccinations later than infancy, owing to the increasing neglect of vaccination. A similar insusceptibility of infants was noticed in Holland,[10] where the ratio of cases to vaccinations in children under 2 years of age was 1: 13,531, while in children from 3 to 12 years of age the ratio was 1: 3,555. In Germany no particular distribution with relation to age was noticed by Eckstein [40] or by Hamel,[13] most cases occurring in the groups from 1 to 2 years of age on which the most vaccinations had been performed. But Knöpfelmacher pointed out that in four large cities of Germany, 28 per cent of the vaccinations, as opposed to 13 per cent of the cases of postvaccinial encephalitis, were in children under 1 year of age, while 50 per cent of the vaccinations and 40 per cent of the cases of postvaccinial encephalitis occurred in children in their second year of age, apparently showing an increase in susceptibility in the second year. Of the cases in Vienna and lower Austria, none occurred in children under 3 years of age, although one third of the vaccinations were performed on children under 2.[16]

From these or similar figures a number of authors have concluded that children of school ages are relatively very susceptible to the disease. From the figures at my disposal, no comparison other than that of early infancy with other ages can be made. Whether adults are more or less susceptible than school children cannot be determined, but that young infants are definitely less susceptible seems to be established.

A number of cases have been reported in which children were ill just previous to, or at the time of, vaccination, which suggests that a general lessening of resistance might be a factor in the occurrence of the complication. Coyl and Hurst [46] and Horder [47] reported cases occurring in children vaccinated while convalescing from pneumonia, or while still weak from infectious disease. It is, of course, possible that these cases were coincidental, since it is probable that many children are vaccinated under similar conditions with no evil effects.

There is no indication of any seasonal occurrence, the time of appearance apparently depending on the seasonal variations in vaccinations. The great majority of cases have occurred in northern Europe, but a number have been reported in Italy,[22] and at least one case has occurred in the tropics.[23]

MORBID ANATOMY

That the pathologic picture presented by the postvaccinial cases of encephalitis is constant and typical and can be definitely differentiated from that of poliomyelitis and that of epidemic encephalitis is

46. Coyl, C. D., and Hurst, E. W.: Lancet **2**:1246, 1929.
47. Horder, Thomas: Lancet **1**:1301, 1929.

accepted by most investigators. Turnbull [48] gave a complete résumé of his own observations and those of McIntosh [2] and correlated them with the descriptions of Bastiaanse [5] (1925), Perdrau [49] (1928), Schurman [50] (1928) and Lucksch [36] (1927). The distribution of the lesions is typical and constant. Focal changes occur throughout the central nervous system from cortex to lumbosacral cord. The white and gray matter are both extensively involved. The meninges are only slightly affected, the characteristic changes occurring within the central nervous system. The essential lesions are perivascular and marginal zones of demyelinization and perivascular infiltration, largely extra-adventitial. The demyelinization is almost always around veins and extends for long distances along their branches; it is usually complete, only a fraction of the axis cylinders surviving in any zone. In the acute cases a great number of proliferated glial cells are usually contained in the wide-meshed net of glial fibrils in the zones of demyelinization. Proliferated glial cells extend a variable distance beyond the zones of demyelinization and cause a diffuse infiltration in the most severely affected regions. Hemorrhages are rare and, when they occur, are small and perivascular. Tigrolysis in the nerve cells is constant, but complete necrosis is rare, and neuronophagia is seldom, if ever, seen.

McIntosh and Scarff [51] had a different conception of the essential lesions, which becomes important later in the comparison of experimental vaccinial encephalitis in animals with the postvaccinial disease. They considered the essentially characteristic feature to be the radiating infiltration of parenchyma by large endothelial cells with clear, oval nuclei. These cells occur in an apparent radiating growth out from the central mass and give an appearance like that of a tissue culture. The demyelinization was considered by McIntosh to be of secondary importance. Coyl and Hurst [46] and Taylor [52] reported cases conforming to the foregoing general description from Turnbull. Taylor considered the infiltration to be made up chiefly of endothelial cells. In this country, the cases of Wilson and Ford,[24] Fulgham and Beykirch (studied by Flexner [38]) and Tuthill [26] conform to the same general picture.

POSSIBLY RELATED CONDITIONS

There are a number of pathologic conditions occurring independently or as complications of other diseases which on clinical or pathologic grounds have been regarded as identical with, or closely related to,

48. Turnbull, H. M.: Brit. M. J. **2**:331, 1928.
49. Perdrau, J. R.: J. Path. & Bact. **31**:17, 1928.
50. Schurman, Paul: Beitr. z. path. Anat. u. z. allg. Path. **79**:409, 1928.
51. McIntosh, J., and Scarff, R. W.: Proc. Roy. Soc. Med. **21**:705, 1928.
52. Taylor, J. F.: Lancet **1**:1302, 1929.

the encephalomyelitis following vaccination. Smallpox, measles, chickenpox, German measles, mumps, scarlatina, whooping cough, typhoid fever, typhus fever, yellow fever and psittacosis all have been shown to include lesions of the central nervous system, either as an integral part of the disease or as an occasional complication. Conditions in which the symptoms or lesions were possibly very similar to those of the postvaccinial diseases have occurred following antirabic treatment and also as apparent clinical entities independent of any known disease as an exciting factor. Greenfield [53] took over the term "acute disseminated encephalomyelitis" from Westphal to describe a group of these conditions which he regarded as proved on pathologic grounds to be very similar. He included in this group only conditions following vaccinia, variola and measles, and some independent forms. He considered that there is no satisfactory evidence that the pathologic picture in the other cases is the same.

Encephalomyelitis Complicating Smallpox.—Aldrich,[54] in 1904, collected from the literature the reports of cases of smallpox in which there was involvement of the central nervous system and added several previously unrecorded. He stated that cases of smallpox complicated by paralysis have been recorded since the disease passed from tradition to record. The occurrence of postvaccinial encephalitis has aroused interest in these cases, and adequate summaries of the literature have been given by Turnbull and McIntosh,[2] Wilson and Ford,[24] and Troup and Hurst.[55] Troup and Hurst studied the records of mortality from smallpox in England and Wales from 1925 to 1929. Of 140 deaths in 51,243 cases of smallpox, 23 were ascribed to conditions of the central nervous system. The diagnoses in six of these cases indicated that the condition was encephalitis. Schamberg and Kolmer,[56] among the records of 3,000 cases of smallpox, found 8 in which there was mention of paralysis, and Rolleston,[57] among the records of 10,000 in the London epidemic of 1921 and 1922, found only 25 in which there was note of nervous complications.

On clinical grounds the cases have been divided into several groups according to the area of the central nervous system involved. Apparently the most frequent type is that in which paralysis of the legs without other symptoms occurs. The paralysis is usually flaccid, and muscular wasting and loss of reflexes occur. The

53. Greenfield, J. G.: A System of Bacteriology, London, Medical Research Council, 1930, vol. 7, p. 133.

54. Aldrich, C. J.: Am. J. M. Sc. **127**:198, 1904.

55. Troup, A. G., and Hurst, E. W.: Lancet **1**:566, 1930.

56. Schamberg, J. F., and Kolmer, J. A.: Acute Infectious Diseases, ed. 2, Philadelphia, Lea & Febiger, 1928, p. 241.

57. Rolleston, J. D.: Acute Infectious Diseases, London, Heinemann, 1929, p. 379.

symptoms may be entirely bulbar, with dysarthria and disturbances of swallowing, or these symptoms may be combined with spastic weakness, ataxia and sometimes mental changes, indicating a more diffuse involvement resembling disseminated sclerosis. According to Troup and Hurst,[55] the mode of onset may suggest transverse myelitis, and only later a certain degree of weakness of the arms and drowsiness indicate involvement of the upper part of the central nervous system. The picture in this later extension differs from that in the postvaccinial cases, in which as a rule there is no progression after the first symptoms. In the great majority of variolar complications, the nervous symptoms appear before the sixteenth day of the disease, and in some cases, even before the eruption appears. Partial or complete recovery is the rule, but permanent disturbances are more frequent than with the postvaccinial condition. That the complications are not due to especially neurotropic strains of virus is indicated by the report of Troup and Hurst [55] in which a case with, and fifteen cases without, nervous complications were contracted from the same source of infection.

McIntosh,[58] McIntosh and Scarff,[51] and Troup and Hurst [55] found that the pathologic picture in the cases reported by them could not be differentiated from that described as characteristic of the postvaccinial cases. McIntosh found the tissue-culture-like arrangement of endothelial cells which he described as occurring in postvaccinial encephalitis even more pronounced in encephalitis of variolar origin.

Encephalomyelitis Complicating Measles.—Comprehensive reviews of the literature on the occurrence of nervous complications of measles are contained in papers by Ford [59] (1928) and Greenfield [60] (1929). Greenfield emphasized the fluctuation in the incidence of these complications. Sydenham, in his description of the epidemics of 1670 and 1674, made no mention of nervous sequelae, but cases were described by Lucas (1790), Abercrombie (1845) and Barlow and Penrose (1886), and a small outbreak occurred in London in 1904 and 1905. In recent years, since 1924, there has been another period of increased incidence, with cases occurring on the continent and in America. Reports of individual cases from England, France and Germany in the interval indicate that the disease had not disappeared entirely during the intervening years. Boenheim,[61] summarizing the observations in 5,940 cases of measles in the Berlin hospitals from 1905 to 1925, found the incidence of nervous complications to be 4 per thousand cases.

Clinically, the cases are grouped according to the area of apparent involvement. There may be only cerebral symptoms of brief duration from which recovery is complete, or these may be combined with neurologic disturbances that are not revealed until the cerebral phase passes. Paraplegias indicating involvement of

58. McIntosh, James: Brit. M. J. **2**:334, 1928.
59. Ford, F. R.: Bull. Johns Hopkins Hosp. **43**:140, 1928.
60. Greenfield, J. G.: Brain **52**:171, 1929.
61. Boenheim, Curt: Ergebn. d. inn. Med. u. Kinderh. **28**:598, 1925.

the spinal cord may occur alone or in conjunction with cerebral symptoms, indicating a general involvement of the central nervous system. Ataxias indicating cerebellar involvement are common. The onset of the nervous symptoms almost always follows the fever-free interval of from one to two days after the rash is out, that is, about the seventh day of the disease, but it may occur before or at the height of the eruption or may be delayed for from two to three weeks.

The recent descriptions of the microscopic changes are in general agreement. From Wohlwill's descriptions of two cases of measles Turnbull [48] regarded the involvement of the central nervous system in these cases as practically identical pathologically with that in the postvaccinial disease. Greenfield [60] regarded the picture as similar to, if not identical with, that of the postvaccinial complication. The differences lie in the greater amount of perivascular infiltration and the more complete demyelinization in the postvaccinial forms. The distribution of the zones of demyelinization along the margins of the cord and the walls of the ventricles is the same in both conditions. Ford [59] also found a much smaller amount of perivascular infiltration in his cases of measles. Zimmerman and Yannet [62] found little involvement of the gray matter, in contrast with that in the generally accepted picture of the postvaccinial type, in which both gray and white matter are usually extensively involved.

Nervous Complications of Varicella.—Winnicott and Gibbs [63] and Wilson and Ford [24] published summaries of the literature dealing with the nervous complications of chickenpox, with descriptions of cases seen by themselves. More recent observers (Conrad,[64] Bertoye and Garcin,[65] Graham [66]) have added reports of five cases to the round dozen collected by the aforementioned authors. The symptoms are somewhat variable, but can again be classified as indicating involvement of the brain, the brain stem or the spinal cord, or all three. The time of onset of the complications is rather constant, occurring chiefly from the ninth to the thirteenth day of the varicella, but sometimes as early as the fourth or as late as the fifteenth day. Recovery always occurs and is probably invariably complete. Since no autopsies have been performed, the nature of the lesions is unknown.

Nervous Complications of Mumps.—The occurrence of nervous complications of mumps was first noted by Hamilton in 1758. Reports of cases and comprehensive summaries of the literature were published

62. Zimmerman, H. M., and Yannet, Herman: Arch. Neurol. & Psychiat. **24**:1000, 1930.

63. Winnicott, D. W., and Gibbs, N.: Brit. J. Child. Dis. **23**:107, 1926.

64. Conrad, C. E.: Arch. Pediat. **46**:716, 1929.

65. Bertoye, P., and Garcin: Presse méd. **37**:1517, 1929.

66. Graham, Stanley: Arch. Dis. Childhood **5**:146, 1930.

by Haden [67] and Weissenbach, Basch and Basch.[68] The condition had been largely regarded as essentially a meningitis, but Haden showed that the cerebral symptoms were out of proportion to the amount of meningeal reaction, as indicated by the spinal fluid, and could also occur without meningeal signs. Weissenbach, Basch and Basch classified the cases as meningeal or meningo-encephalitic, either complicating typical mumps or occurring independently with only slight clinical or epidemiologic evidence, pointing to the etiologic factor. The onset may precede or follow the parotid swelling, but occurs most often at the height of the parotid lesion. Testicular involvement indicating a generalization of the virus is often associated. The incidence varies considerably; 16 cases have been observed in 653 cases of mumps, but over 1,000 cases of mumps without any nervous complications have been recorded. Few necropsies have been recorded; marked congestion of the brain and serous meningitis apparently were the only changes.

Experimentally, Wollstein [69] and Gordon [70] were able to produce nervous symptoms and lesions in cats and monkeys by the intrathecal and intracerebral injection of bacteria-free filtrates of saliva from patients with mumps. Sections of the brain from one of Gordon's animals showed definite infiltrative evidence of encephalitis, although pronounced degenerative changes in the nerve cells of cortex and anterior horns were the most marked feature.

Other Postinfection Encephalitides.—According to McIntosh,[58] encephalitis is a constant feature of typhus fever and may be regarded as part of the disease. The lesions, consisting essentially of proliferations of large, clear cells into the surrounding nerve tissue, with infiltration by inflammatory cells (plasma cells, lymphocytes and a few polymorphonuclears), are regarded by McIntosh as showing great similarity to the lesions in postvaccinial and postvariolar encephalitis. Cerebral complications are also said to occur in yellow fever,[71] and experimentally, cerebral lesions, consisting of proliferation of the capillary endothelium and perivascular infiltration by mononuclears, were produced in mice by this virus. Encephalitic syndromes have complicated or followed psittacosis (Krichefski,[72] Thompson [73]), rubella

67. Haden, R. L.: Arch. Int. Med. **23**:737, 1919.

68. Weissenbach, R. J.; Basch, Georges, and Basch, Marianne: Ann. de med. **27**:5, 1930.

69. Wollstein, Martha: J. Exper. Med. **34**:537, 1921.

70. Gordon, M. H.: Lancet **1**:652, 1927.

71. Theiler, Max: Science **71**:367, 1930.

72. Krichefski, H. J.: Brit. M. J. **1**:1093, 1930.

73. Thompson, A. P.: Lancet **1**:396, 1930.

(Debie [74]), scarlatina [75] and pertussis (Askin and Zimmerman [76]). Such pathologic investigations as have been described indicate that the encephalitic complications of the two latter conditions are not related to the group of encephalitides complicating vaccination, variola and measles.

Paralysis Complicating Antirabic Treatment.—On the basis of the pathologic picture, the paralyses sometimes complicating antirabic treatment have been considered by some observers to be similar to the postvaccinial disease. A considerable number of antirabic treatments (4,836) had been given before this accident was first noticed in 1887. It was regarded as a paralytic form of rabies until it occurred in a patient proved to have been bitten by a healthy animal. Stuart and Krikorian [77] reviewed the literature and published reports of cases and experimental work. The condition is directly related to the treatment and probably to the injection of diseased or normal brain, since similar conditions can be produced in animals by the injection of normal brain (Remlinger,[78] Schweinberg,[79] Stuart and Krikorian [77]). Individual predisposition of the patient is an important factor; brain-workers are more susceptible than laborers, and Europeans more than natives of the tropics. The League of Nations Conference on Rabies placed the incidence at 0.28 per thousand. The symptoms usually begin about seven days after the beginning of treatment. The peripheral nerves only may be affected, giving local paralyses; or the symptoms may be those of subacute dorsolumbar myelitis or of acute ascending (Landry's) paralysis. Stuart and Krikorian regarded perivascular infiltration by lymphocytes and plasma cells and demyelinization as the essential features. Turnbull [48] referred to descriptions of the condition and stated that the pathology appears to be similar to that of the postvaccinial disease, but that the descriptions are not precise.

Independent Conditions.—On the basis of the demyelinization as the principal pathologic feature a number of independent conditions have been considered as possibly related to postvaccinial encephalitis. Pette [80] regarded acute disseminated sclerosis occurring spontaneously in children and possibly multiple sclerosis as being closely related to

74. Debie, Robert; Turquetz, Roger, and Broca, Robert: Presse méd. **38**:348, 1930.

75. Editorial, Lancet **1**:1191, 1930.

76. Askin, J. A., and Zimmerman, H. M.: Am. J. Dis. Child. **38**: 97, 1929; footnote 75.

77. Stuart, G., and Krikorian, K. S.: Ann. Trop. Med. **22**:327, 1928.

78. Remlinger, P.: Compt. rend. Soc. de biol. **83**:171, 1920.

79. Schweinberg, Fritz: Wien. klin. Wchnschr. **37**:797, 1924.

80. Pette, H.: Centralbl. f. Bakteriol. (Abt. 1) **110** (supp.):134, 1929.

postvaccinial encephalitis. Multiple sclerosis is generally recognized as differing in that the demyelinization is patchy, not following a blood vessel for far, while in the postvaccinial condition the demyelinization extends for long distances along the affected vessel. Greenfield [81] considered Pette's cases on clinical (being subacute and progressive) and on pathologic grounds as being not strictly comparable. He stressed the fact that the postvaccinial encephalitis and that complicating measles do not become progressive. Greenfield himself described two cases of acute paraplegia with influenza-like onset that showed lesions similar in distribution and character to the lesions of the central nervous system in measles and postvaccinial disease. He included these cases in his group of cases of "acute disseminated encephalomyelitis." Brain and Hunter [82] described a group of cases with remarkable clinical similarity to those of postvaccinial disease. In the one fatal case the pathologic changes were those of toxemia and were not similar to those in postvaccinial disease. They referred to a considerable number of similar cases recorded in the literature, in many of which the condition had apparently been of mildly epidemic form.

The relationship of the conditions described to postvaccinial encephalitis is uncertain, with the possible exception of the encephalitides complicating variola and measles and the two independent cases of Greenfield, which apparently presented a similar pathologic picture and could be assumed to be due to the same or similar viruses.

THEORIES REGARDING THE ETIOLOGY OF POSTVACCINIAL ENCEPHALITIS

Accidental Relationship.—Several possible explanations have been advanced for the occurrence of encephalomyelitis complicating vaccination. While not widely held and probably conclusively disproved, the view that the condition has an accidental relationship to vaccination must first be considered. The small, irregular incidence of the disease at first suggests that the connection is coincidental, and it might be maintained that the nervous lesions are caused by some of the known encephalitogenic viruses or some other unknown factor operating in the patient, by chance, at the time of vaccination. The evidence against this view has been largely presented in the sections on epidemiology and pathology, but will be briefly restated here. Clinically, the majority of cases show a considerable degree of similarity, and the condition is accepted as a definite clinical entity which can be differentiated from epidemic encephalitis and poliomyelitis. The marked constancy of the

81. Greenfield, J. G.: J. Path. & Bact. **33**:453, 1930.

82. Brain, R. W., and Hunter, Donald: Lancet **1**:221, 1929.

period of incubation in itself is possibly sufficient to rule out the theory of fortuitous occurrence. The definite, though not direct, relationship of incidence to the number of vaccinations performed further supports the assumption that there is an actual causal relationship between vaccination and nervous complications. Greenwood's calculations [8] show that the number of deaths from acute nervous disease in the vaccinated group at the time of the maximum occurrence of postvaccinial cases in England was higher than would be probable if the deaths were due to the chance occurrence of the nervous disease in the vaccinated persons. With the possible exceptions of poliomyelitis in England and epidemic encephalitis in the early Dutch cases, there has been no association of postvaccinial encephalitis with other epidemic nervous disease that might suggest an overlapping with these diseases. The constant pathologic picture not related to that of poliomyelitis or to that of epidemic encephalitis and similar only to that of the few conditions mentioned rules out the possibility of the condition being poliomyelitis or epidemic encephalitis.

While a definite causal connection between vaccination and the majority of the reported nervous disorders may be accepted, it is probable [83] that some of the conditions regarded as being "propter," as well as "post," vaccinial, are due merely to inaccurate diagnosis plus a fortuitous relationship. Reisch [84] reported an epidemic that appeared in both vaccinated and unvaccinated children which, with insufficient investigation, could have been regarded as a true postvaccinial disease, since the only fatal case was in a vaccinated child. Grey and Whitaker [85] performed an autopsy in a case reported clinically as postvaccinial encephalitis and found staphylococcal septicemia with multiple pyemic abscesses on the surfaces of the brain. A case cannot be finally regarded as due to vaccination unless epidemiologically, clinically and pathologically it accords with the typical cases considered in foregoing paragraphs. It is inevitable that a number of nervous diseases should manifest themselves coincident with a procedure carried out on such a large scale as vaccination.

Since it is generally admitted and probably proved that certain cases of encephalomyelitis are attributable to vaccination, there remains to be discussed the possible ways in which vaccination might cause these complications. Three hypotheses have been put forward:

1. The nervous lesions are caused by the direct action of vaccine virus on the central nervous system.

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83. Gins, H. A.: Med. Welt **3**:1277, 1929.
84. Reisch, O.: Wien. klin. Wchnschr. **43**:103, 1930.
85. Grey, T. F., and Whitaker, W. M.: Brit. M. J. **1**:1125, 1930.

2. The nervous lesions are not caused by the vaccine virus, but by some other virus or bacterium introduced with the vaccine virus or already present, dormant, in the vaccinated person and activated by the vaccine virus or by the decrease in resistance of the patient brought about by the febrile reaction.

3. The complication is the result of an anaphylaxis-like reaction to the virus or to a nonspecific factor.

The discussion of the evidence in favor of or against these theories will be taken up in the order given.

Vaccine Virus as the Direct Cause.—The production of nervous symptoms and lesions in animals by certain strains of vaccine virus and the fact that many of the filtrable viruses or closely related forms can cause encephalitis in human beings or experimentally in animals are the primary bases on which this theory is founded. It was formerly considered that infection with vaccine virus was a local phenomenon, the virus growing in dermal tissue and only incidentally overflowing into the blood. It is now known that vaccine virus can be recovered from the blood and organs of animals and man for a number of days after inoculation, and that the virus will grow in many different tissues.

Marie,[86] in 1920, showed that vaccine virus injected intracerebrally into rabbits would kill them, giving rise to nervous symptoms, with apparent growth of the virus in the brain. Levaditi, Harvier and Nicolau,[87] in 1921, by a process of adaptation through alternate testicle and brain passage, repeated Marie's work and was able to produce a fixed "neurovaccine" which he could pass indefinitely in series through rabbits' brains. Many workers since then (Condrea,[88] Krumbach,[89] Blanc and Caminopetros,[90] von Wasielewski and Winkler,[91] Bachman and Biglieri,[92] Ledingham [93]) have shown that with many strains of virus, at least, no process of adaptation is necessary: that intracerebral injection of calf virus will produce symptoms and death, and that such viruses can be passed indefinitely from brain to brain. Others have had difficulty [58] in adapting, or have been entirely unable to adapt,

86. Marie, A.: Compt. rend. Soc. de biol. **83**:476, 1920.

87. Levaditi, C.; Harvier, P., and Nicolau, S.: Compt. rend. Soc. de biol. **85**:345, 1921.

88. Condrea, P.: Compt. rend. Soc. de biol. **86**:897, 1922.

89. Krumbach, H.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **38**:1, 1923.

90. Blanc, Georges; and Caminopetros, J.: Compt. rend. Soc. de biol. **88**:1020, 1923.

91. von Wasielewski, T., and Winkler, W. F.: Ergebn. d. Hyg., Bakt., Immunitätsforsch. u. exper. Therap. **7**:1, 1925.

92. Bachman, A., and Biglieri, R.: Compt. rend. Soc. de biol. **88**:351, 1923.

93. Ledingham, J. G. G.: J. State Med. **34**:1925, 1926.

some strains with which they were working (Camus,[94] Cattaneo,[95] Thompson [96]). I [96] was unable to adapt to the brain either the Noguchi strain of testicular virus or the New York City Board of Health strain from which the former was derived. But a commercial strain, a descendant of the same New York virus, easily, on first injection and on subsequent passages, produced nervous symptoms and death and multiplied profusely in the brain. Levaditi, Nicolau and Sanchis-Bayarri,[97] and Aldershoff, Pondman and Pot,[98] produced meningoencephalitis in monkeys by the intracerebral injection of virus. The reaction of the skin to vaccine virus grown in brain (so-called neurovaccine) is characteristically more violent and definitely more hemorrhagic that that to ordinary strains of virus (Camus,[94] Aldershoff, Pondman and Pot,[98] Levaditi,[99] Burnet and Conseil,[100] and in my own experience). Neurovaccine is considered by Levaditi [99] to be more neurotropic (to settle more readily in the brain after peripheral inoculation) than other strains, but others have shown that any strain of vaccine virus can often be found in the brain after peripheral inoculation (Blanc and Caminopetros,[90] Huon and Placidi,[101] Barikine, Kompaneez, Zakharoff and Barikine,[102] Hach,[103] Minervin and Schmerling [104]). In attempting to produce encephalitis in rabbits by peripheral inoculation, many workers have had negative results (Condrea,[88] Cattaneo,[95] Demme,[105] Walthard,[106] Olitsky and Long [107]), but some were occasionally successful (Bachman and Biglieri,[92] Levaditi,[99] Huon and Placidi,[101] Rhoades,[108] McIntosh and Scarff,[109] Hoffmann [110]). Clear-

94. Camus, M. L.: Bull. Acad. de méd., Paris **90**:79, 1923.

95. Cattaneo, L.: Policlinico (sez. prat.) **35**:759, 1928.

96. Thompson, Richard: Proc. Soc. Exper. Biol. & Med. **26**:559, 1929.

97. Levaditi, C.; Nicolau, S., and Sanchis-Bayarri, V.: Presse méd. **35**:161, 1927.

98. Aldershoff, A.; Pondman, A. B., and Pot, A. W.: Ann. Inst. Pasteur **43**:1268, 1929.

99. Levaditi, C.: J. State Med. **32**:151, 1924.

100. Burnet, E., and Conseil, E.: Compt. rend. Soc. de biol. **90**:1408, 1924.

101. Huon and Placidi: Compt. rend. Soc. de biol. **91**:308, 1924.

102. Barikine, W.; Kompaneez, A.; Zakharoff, A., and Barikine, O.: Compt. rend. Soc. de biol. **90**:1134, 1924.

103. Hach, I. W.: Ztschr. f. Hyg. u. Infektionskr. **104**:569, 1925.

104. Minervin, S., and Schmerling, A.: Centralbl. f. Bakteriol. (Abt. 1) **99**:558, 1926.

105. Demme, Hans: Ztschr. f. Immunitätsforsch. u. exper. Therap. **55**:191, 1928.

106. Walthard, B.: Schweiz. med. Wchnschr. **56**:854, 1926.

107. Olitsky, P. K., and Long, P. H.: J. Exper. Med. **48**:379, 1928.

108. Rhoades, C. P., quoted by Flexner (footnote 38).

109. McIntosh, J., and Scarff, R. W.: J. Path. & Bact. **33**:483, 1930.

110. Hoffmann, D. C.: J. Exper. Med. **53**:43, 1931.

kin [111] succeeded in producing symptoms and lesions of the brain by intradermal inoculation of vaccine virus into wild African monkeys.

In view of the peculiar characteristics of the lesions of the skin produced by neurovaccine, Camus [94] suggested that its ability to produce cerebral lesions may be due to its admixture with some contaminating virus. The apparent impossibility of adapting certain strains of vaccine virus to the brain might be interpreted as supporting this conception. Lack of immunity relationships between neurovaccine and herpes virus [112] indicates that the possible contaminant cannot be herpes virus. Addition of a poliomyelitic virus to a nonencephalitogenic strain of vaccine virus did not render this strain encephalitogenic for rabbits,[113] suggesting that poliomyelitic virus is not the supposed additional virus. All attempts, by passage through animals immune to a nonencephalitogenic strain of vaccine virus, to separate from neurovaccine some nonvaccinal factor which, when added to the nonencephalitogenic virus, would produce a neurovaccine have been unsuccessful.[114] All the evidence at one's disposal indicates that the neurovaccines are not contaminated viruses, but vaccine viruses that have acquired the ability to grow in nervous tissue. This change cannot always be produced at will, but may occur spontaneously, as in the commercial strain of virus referred to. It is possibly associated with an increase in generalizing power, but not necessarily in virulence for the skin as measured by titration by dilution.

The evidence supporting the hypothesis that the human postvaccinial condition is an expression of this encephalitogenic power of vaccine virus which has been described will now be considered.

Epidemiologic Evidence: The constancy of the relationship between the onset of symptoms and the time of vaccination which has been stressed is regarded by the proponents of the theory that vaccine virus is the direct cause as indicating the vaccinial nature of the nervous lesions. There are, however, other possible explanations of the constant period of incubation. An activated virus introduced at the time of vaccination would also probably be characterized by a fairly regular period of incubation. However, all attempts to show the presence of any known virus in the lymphs used have failed, although Perdrau [115] showed that herpes and vaccinia could be carried along together in animal passage. The lack of evidence incriminating any particular batch or batches of lymph also indicates that the encephalitis is not due to contamination of the lymphs. It is possible [3] that the so-called constancy of the period of incubation may be more apparent than real, owing to the fact that the constitutional symptoms present just

111. Clearkin, P. A.: Brit. J. Exper. Path. **11**:329, 1930.

112. Holden, M., and Thompson, Richard: Unpublished work; Olitsky and Long (footnote 107).

113. Thompson, Richard: J. Exper. Med. **51**:777, 1930.

114. Thompson, Richard; and Buchbinder, Leon: Unpublished work.

115. Perdrau, J. R. (footnote 3).

before the reaction to the vaccination reaches a maximum may call attention to cerebral symptoms for the first time.

The similarity of the periods of incubation in postvaccinial encephalitis, variola and generalized vaccinia in man has been considered as evidence in favor of the vaccinial nature of the postvaccinial disease.[44] It is regarded as probable that the mechanism is the same in each case; a local multiplication of the virus with secondary generalization producing the general disease in smallpox, the lesions of the skin in generalized vaccinia and the changes in the central nervous system in postvaccinial encephalitis. The fact that the generalization of the virus, as indicated by the positive results from examination of the blood, is probably at its height at about the same time also favors this view (McIntosh[116]).

Netter[117] stated that the disease occurs after revaccination in a much smaller percentage of cases than after primary vaccination and regards this as evidence favoring the theory that vaccine virus is the direct cause, since the revaccinated persons have a degree of vaccinial immunity. Statistical data comparing the incidence of the complication in the two groups are not available, but the general impression seems to support Netter's views as to the comparatively rare occurrence in revaccinated persons. The information regarding the occurrence of a previously successful "take" is not always reliable, but there have been a number of cases reported as following probably authenticated revaccination (Hamel,[13] Mader,[118] Rosendahl,[119] Hekman[120]). Hekman[120] reported a number of cases following revaccination and stated that in these cases the period of incubation was shorter than in cases following primary vaccination. He regarded this as further evidence of the vaccinial nature of the disease, comparing the acceleration to the shortening of the period of incubation in varioloid and vaccinoid. It is indeed difficult to explain the shorter period of incubation on any other basis, but here again one lacks conclusive statistical evidence of an accelerated process. It would be interesting to determine whether more cases have followed revaccination in Germany than in other countries, accounting for the shorter average period of incubation in that country.

Isolation of Vaccine Virus from the Nervous System in Cases of Postvaccinial Encephalitis: The results of experimental and pathologic

116. McIntosh, James: Lancet **1**:618, 1930.

117. Netter, A., quoted by Paris correspondent: Vaccinal Encephalitis, J. A. M. A. **93**:2040, 1929.

118. Mader, A.: Jahrb. f. Kinderh. **123**:111, 1929.

119. Rosendahl, H. M.: Nederl. tijdschr. v. geneesk. **73**:5117, 1929; abstr., Bull. Hyg. **5**:236, 1930.

120. Hekman, M. J.: Tribuna med. **64**:307, 1930.

investigation of postvaccinial encephalitis have been used by all the proponents of theories to support their respective views. A crucial point in favor of the theory the vaccine virus is the direct cause would be the presence of vaccinia virus in considerable amounts in the brain in fatal cases, since in rabbits, when encephalitis occurs, there is a profuse increase of virus in the brain. While a small number of workers have reported the presence of vaccine virus in the brain in fatal cases (Turnbull and McIntosh,[2] McIntosh and Blaxall,[121] Aldershoff,[122] Bijl[123]), it has usually been in small amounts and detected only after enrichment by passage through the testicle. Many workers have had entirely negative results (Luksch,[4] Perdrau,[115] Fildes,[124] Bastiaanse, Bijl and Terburgh,[125] Levaditi, Lepine and Troisier,[126] Maitland,[127]). While the supporters of the theory that the disease is due to activation of another virus regard the presence of the virus in the brain in small amounts as a probable concomitant of normal vaccination, the supporters of the theory that vaccine virus is the direct cause would explain its absence, in those cases in which it is not found, on the basis of autosterilization as expounded by Levaditi to explain the absence of herpes virus from the brain in cases of epidemic encephalitis (Netter[128]). Bijl and Fraenkel[129] reported that the brain in a fatal case did inactivate vaccine virus, giving a modicum of support to the explanation by autosterilization. Using cerebrospinal fluid for which normal vaccinated controls were available, Herzberg-Kremmer and Herzberg[130] found vaccine virus in one of three cases of postvaccinial encephalitis, although eighteen normal controls were negative. Gildemeister[131] also found no virus in the cerebrospinal fluid of fifteen normal vaccinated persons, but found it in the fluid of one of four cases of postvaccinial disease. Widowitz[15] found that the serums in two cases of postvaccinial encephalitis had

121. McIntosh, J., and Blaxall, F. R. (footnote 3).

122. Aldershoff, H.: Acta path. et microbiol. Scandinav., 1930, supp. 3, p. 9.

123. Bijl, J. P.: Versl. med. Volksgezdh., 1927, p. 1471; quoted by Netter, Presse med. **37**:1469, 1929.

124. Fildes, P. (footnote 3).

125. Bastiaanse, F. S. van B.; Bijl, J. P., and Terburgh, J. T.: Geneesk. tijdschr. v. nederl. Indie **70**:1267, 1926.

126. Levaditi, C.; Lepine, P., and Troisier, J.: Bull. Acad. de méd., Paris **100**:818, 1928.

127. Maitland, C. (footnote 3).

128. Netter, A.: Bull. Acad. de méd., Paris **102**:255, 1929.

129. Bijl, J. P., and Fraenkel, H. S.: Centralbl. f. Bakteriol. (Abt. 1) **112**:412, 1929.

130. Herzberg-Kremmer, H., and Herzberg, Kurt: Centralbl. f. Bakteriol. (Abt. 1) **115**:271, 1930. Eckstein, A.; Herzberg-Kremmer, H., and Herzberg, Kurt: Deutsche med. Wchnschr. **56**:264, 1930.

131. Gildemeister, E.: Deutsche med. Wchnschr. **55**:1372, 1929. Gildemeister, E., and Hilgers, Paul: Centralbl. f. Bakteriol. (Abt. 1) **117**:322, 1930.

considerably less power of neutralizing the vaccine virus than did the serums of persons who were vaccinated about the same period of time before the withdrawal of serum, possibly indicating that the invasion of the brain is the result of an insufficient immunity reaction to the dermal infection. Efforts to detect the presence of other viruses in the brain in cases of postvaccinial encephalitis have been without result (herpes,[132] poliomyelitis [133]).

Are the lesions vaccinial? The similarity or dissimilarity of the lesions of brain and spinal cord in postvaccinial encephalitis and in experimental vaccinial encephalitis in animals is obviously of importance in determining the part played by vaccine virus in the etiology of the former. The essential pathology of the human disease has been briefly reviewed earlier in this paper. Levaditi and his co-workers [134] described the cerebral lesions resulting from the intracerebral inoculation of neurovaccine into rabbits and apes. They described the process as a meningo-encephalitis with involvement of the dura, pia mater and cortex. Perivascular and focal infiltration of these structures, first by polymorphonuclear cells and later by mononuclears, takes place. Condrea [88] gave a similar description, but also described Guarnieri's bodies as occurring in the nerve cells. Hurst and Fairbrother [135] regarded the essential lesion resulting from intracerebral inoculation of vaccine virus into rabbits and monkeys as a fibrinous, hemorrhagic and polymorphonuclear meningitis. They contrasted this picture with that in postvaccinial encephalitis, stressing in the latter the slight meningeal reaction, the strictly perivascular distribution of the lesions, the occurrence and the rapidity of demyelinization, the microglial nature of the infiltration and the rarity of true perivascular infiltration by lymphocytes and plasma cells. They concluded that the pathologic pictures in the two diseases are so different as to make it extremely unlikely that vaccine virus is the cause of the postvaccinial condition.

On the other hand, in a number of studies McIntosh and his co-workers maintained that the lesions in postvaccinial encephalitis are essentially similar to those in vaccinial encephalitis in animals, to those in the various organs in generalized vaccinia in rabbits, to those in the brain in postvariolar encephalitis and to the focal lesions in smallpox.[136] In one case of postvaccinial encephalitis, McIntosh found a similar picture in the multiple lesions occurring in the internal organs. McIntosh

132. Maitland and Perdrau (footnote 3). Bijl, J. P., quoted by Gildemeister (footnote 44).

133. Levaditi, C., and Bijl, J., quoted by Gildermeister (footnote 44).

134. Levaditi and co-workers (footnotes 87 and 97).

135. Hurst, E. W., and Fairbrother, R. W.: J. Path. & Bact. **33**:463, 1930.

136. McIntosh, James; and Scarff, R. W.: J. Path. & Bact. **32**:551, 1929. McIntosh and Scarff (footnote 51). McIntosh (footnote 58).

and Scarff [109] did not regard the fibrinopurulent meningitis described by Hurst and Fairbrother as characteristic of vaccinia either in the skin or in the brain. With vaccine virus they produced in rabbits, two types of lesions, meningitis and meningo-encephalitis. They considered the difference between these as primarily one of severity. The presence of a diffuse radiating infiltration by a large number of cells with large, clear nuclei, giving the appearance of a tissue culture, was regarded as the characteristic feature of all the lesions mentioned. Demyelinization was not regarded by McIntosh as of especial importance as a distinguishing factor, since it occurs in several unrelated pathologic conditions and has been observed by him in vaccinial encephalitis in the rabbit and monkey. Clearkin [111] found the picture described by McIntosh in the brains of wild monkeys inoculated intradermally with vaccine virus. He also found some degree of perivascular demyelinization and regarded the lesions as essentially similar to the human postvaccinial lesions. Bijl and Fraenkel [129] were of the same opinion as McIntosh, that the histologic picture in the brain in postvaccinial encephalitis is essentially similar to that produced in the organs of rabbits by vaccine virus. Spooner [137] in a recent study found meningitis to be the most conspicuous lesion following injection of neurovaccine into the rabbit's brain. While certain changes occurred in the myelin sheaths, perivascular demyelinization of the kind described in postvaccinial encephalitis was not seen. Agreeing with McIntosh as to the damage to, and proliferation of, the vascular endothelium Spooner regarded this feature as subsidiary to the general inflammation. The final decision regarding the vaccinial or nonvaccinial nature of the postvaccinial lesions awaits further reports confirming or denying McIntosh's descriptions.

Serum Treatment: Serum from vaccinated persons or animals has been used in treatment in a number of cases of postvaccinial encephalitis, with apparent benefit (Horder,[47] Rozendahl,[110] Hekman,[138] Netter [139]). The apparent beneficial action of this serum was regarded by Netter, among others, as a further demonstration of the vaccinial nature of the disease. However, controls treated with normal serum are not available, and statistical proof of the efficiency of the serum from vaccinated persons or animals is not yet possible, making its action rather unreliable evidence as to the etiology of the disease.

Some authors upholding the theory that vaccine virus is the direct cause have explained the increase in incidence of postvaccinial encephalitis in recent years by

137. Spooner, E. T. C.: Am. J. Path. **6**:767, 1930.

138. Hekman, J.: Nederl. tijdschr. v. geneesk. **73**:4774, 1929; Med. Welt **4**: 247, 1930.

139. Netter, A.: Tribuna med. **64**:307, 1930; Presse méd. **37**:1469, 1929.

assuming some change in the virus caused by its passage through rabbits, which is a comparatively recent procedure. Coplans, King and Simpson [140] emphasize the fact that encephalitis first occurred in England subsequent to the use of rabbit lymph. Netter [139] (1930) also connected the disease with the passage of the virus through rabbits. Other than the "post hoc" type, there seems to be no evidence in favor of this view. Neurovaccine passed through many generations of rabbits in Spain produced no encephalitis, although it did in Holland.[141] The only kind of lymph the use of which in Holland has not been followed by encephalitis is a rabbit strain from the Dutch East Indies.[11] A lymph from Japan and a bovine lymph from Switzerland, which had never been through rabbits, have been associated with encephalitis in Holland.[141]

Possibly the majority of the investigators concerned with the problem of postvaccinial encephalitis have been unable to accept the theory that vaccine virus is the cause for a number of reasons. Two of these have been discussed, involving the rarity or the lack of virus in the brain in fatal cases and the differences between the lesions in experimental encephalitis in animals and those in the postvaccinial disease. In the field of epidemiology there are a number of facts that are regarded as incompatible with this theory. The sudden and recent increase in incidence was cited by both the Andrewes and Rolleston committees as making it unlikely that vaccine virus is the only factor in the etiology. Many different strains of lymph have been associated with the complication, and it was considered extremely improbable that all these strains simultaneously acquired the property of producing changes in the central nervous system. The extremely irregular occurrence and the lack of direct proportionality of incidence to number of vaccinations also indicate the existence of some factor in addition to that of vaccine virus. The continued use, in Spain, of a strain of virus adapted to the brain of the rabbit (neurovaccine of Levaditi) for over two million vaccinations without the occurrence of a single case of encephalitis seems to indicate that the conditions in man and animal have no relationship, although it has been pointed out that when this strain was taken to Holland, a possibly greater proportion of cases resulted than when dermal strains were used.[117]

Some observers [135] have considered their inability to produce lesions in the brains of rabbits by cutaneous infection as evidence against the direct rôle of vaccine virus in the postvaccinial disease, but, as noted heretofore, others have occasionally been successful, and it must be pointed out that in human beings, in whom the cutaneous route of inoculation is always used, the incidence is extremely low (from 1 in 4,000 to 1 in 50,000).

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140. Coplans, M.; King, W. G., and Simpson, W. J. R.: Brit. M. J. **2**:556, 1929.

141. Paschen, E.: Deutsche med. Wchnschr. **56**:219, 1930.

The epidemiologic features considered by many as making unlikely the hypothesis that vaccine virus is the cause do not seem to eliminate the possibility of direct action of vaccine virus in postvaccinial encephalitis. The supporters of this theory do not maintain that the inoculation with vaccine virus is the only factor in the disease. McIntosh, in his minority report to the Andrewes committee, stressed the presence of an "accessory factor," and Netter [142] mentioned the possibility of some peculiar "individual susceptibility" as explaining many of the epidemiologic peculiarities of the disease. Aycock,[143] in his studies on poliomyelitis, emphasized the fact that all who were exposed to the virus do not contract the disease, but that the majority are immunized without recognizable symptoms. He presented data that indicate that these different reactions to infection with the virus may be due to variations in the physiology of the hosts rather than to variations in the virus. The variations and the irregularity of the incidence of postvaccinial encephalitis might be explained on this basis. Zinnser [144] pointed out that the postvaccinial complication has occurred much more frequently in the northern than in the southern countries of Europe and has suggested that deficiency of vitamins might explain the differences in susceptibility.

ACTIVATION OF SOME OTHER VIRUS

The Andrewes Committee [3] referred to the activation of some concurrent infections, such as leprosy, by vaccinia and on this analogy based their suggestion of a possible activation of some virus, known or unknown, causing postvaccinial encephalitis. The fact that no known virus, other than that of vaccinia, has ever been isolated from the brain in fatal cases appears to indicate that the supposed activated virus is one at present unknown. Kraus and Takaki [145] claimed that by a special technic for the fixation of alexins they had demonstrated in one fatal case the presence of a virus related to herpes, but their work has not been confirmed. The most convincing evidence that the postvaccinial condition is caused by the activation of some unknown virus is found in the clinically and possibly pathologically similar conditions occurring independently and following other exanthems. These conditions have been described in some detail, and it has been emphasized that only in the cases following smallpox and measles and possibly some independent cases has a definite histologic similarity to postvac-

142. Netter, A., quoted by Paris correspondent, J. A. M. A. **93**:858, 1929.

143. Aycock, L. W.: J. Prev. Med. **3**:245, 1929.

144. Zinnser, H.: Carpenter Lecture, New York Academy of Medicine, 1930.

145. Kraus, R., and Takaki, J.: Med. Klin. **21**:1872, 1925. Kraus, R.: Wien. klin. Wchnschr. **40**:185, 1927.

cinial encephalitis been proved. McIntosh considered cerebral complications of smallpox as evidence of the vaccinial nature of postvaccinial encephalitis and regarded cases of encephalitis in measles as similar because caused by a virus having properties similar to the variola-vaccine viruses. The recent increase in the incidence of these similar conditions coincidental with the appearance of the vaccinial complication is stressed by the supporters of the activation theory,[146] who consider it difficult to assume a sudden rise in the encephalitogenic properties of all these viruses simultaneously. But it is likely that changes in individual susceptibility to one encephalitogenic virus would also make for greater susceptibility to other similar viruses, so that it is not necessary to assume a second virus to explain these coincidental variations in incidence. The Andrewes committee [3] considered the irregular grouping of postvaccinial cases as indicating the occurrence of small foci of carriers of a neurotropic virus activated by the vaccinations. Knöpfelmacher suggested that the supposed greater susceptibility of children of school age is due to the greater exposure of these children to possible encephalitogenic viruses. Greenfield [60] quoted a case reported by Lucas in which variolar encephalitis and encephalitis complicating measles occurred in the same patient some years apart and suggested this as evidence of activation of a latent virus; but possibly a more plausible explanation would be that the patient had a peculiar susceptibility to these encephalitogenic viruses. The cases occurring in the same families at long intervals could be explained on the same basis. On the experimental side Zurukzoglu [147] and Levaditi and Nicolau [148] attempted to show that vaccine virus is capable of activiating subinfective doses of herpes virus, but Maitland and Gordon [149] were unable to confirm this.

The activation of, or the introduction of, bacteria or other larger forms by vaccination has been considered, but the great majority of workers have been unable to cultivate bacteria from the brain or cerebrospinal fluid in cases of postvaccinal encephalitis. Cases have been produced by the use of bacteriologically sterile neurovaccine, ruling out the introduction of bacteria by the lymph. Certain workers, however, have obtained results that suggest the activation of bacteria. Bijl (Gildemeister [44]) isolated from the brain in two cases a pleomorphic streptococcus that produced fatal encephalitis on intracerebral injection into rabbits. The lesions were not like the lesions in postvaccinial encephalitis, however. Aldershoff and Pondman [150] isolated Bacillus bipolaris from the lymph used and from the nasal discharges in a case. They proved that intracerebral vaccination in rabbits

146. Greenfield (footnotes 53 and 81).

147. Zurukzoglu, S.: Klin. Wchnschr. **6**:70, 1927.

148. Levaditi, C., and Nicolau, S.; Compt. rend. Soc. de biol. **93**:3, 1925.

149. Maitland and Gordon (footnote 3).

150. Aldershoff, H., and Pondman, A. B. F. A.: Centralbl. f. Bakteriol. (Abt. 1) **107**:433, 1928.

activated B. bipolaris already present and were able to isolate the organism from the brains of these rabbits. Pondman and Pette (Gildemeister [44]) also showed an activation of B. bipolaris in vaccinated rabbits, but showed that it could produce only meningitis and not encephalitis. Kling, Lonberg and Wassen [16] found in the brain in fatal cases some round and oval bodies which they regarded as protozoa and considered were activated by the vaccination, and caused the cerebral lesions. Recently Aldershoff [151] reported finding certain yeast cells in the throats of persons with postvaccinial encephalitis and of contacts and in the cerebrospinal fluid of one, but never in the lymph used. Intravenous injections of the cultures of these organisms produced nervous symptoms in rabbits. A monkey nasally infected with the organisms showed nervous symptoms, and the yeast cells were found in the brain. The organism was found in the brain in six of eight postvaccinial cases and in poliomyelitic material which Aldershoff obtained from the Pasteur and Rockefeller Institutes. He considered this organism to be related to, if not identical with, the globoid bodies of Flexner, the streptococcus of Rosenow and the protozoon of Kling.

The assumption of a second unknown virus has been objected to by McIntosh on the ground that it introduces an unnecessary complication. It is, however, necessary to assume some factor in addition to vaccination to explain the peculiarities of the epidemiology, and the assumption of a virus might seem to be no more complicating than the assumption of a variation in susceptibility. But it is questionable whether the epidemiology can be explained by the assumption of an activated virus alone. By analogy with the virus of poliomyelitis a virus occurring in so many different areas would in time be generally distributed within these areas (especially the urban), and the irregular distribution of cases would still require a variation in susceptibility for its explanation. The lack of multiple cases in the same family, a feature of the postvaccinial disease, as well as of poliomyelitis, is much more easily explained by a difference in susceptibility than by the assumption that one child in the family is infected with the unknown virus, while the others are not.

Allergy.—A third possible etiologic explanation has been advanced by several observers. Starting with the fact that the period of incubation is the same as that required for the development of vaccinial immunity, Glanzman [152] suggested that the changes in the central nervous system result from a local anaphylactic reaction between the virus and the cellular antibodies. The virus in this process is simultaneously destroyed, which explains its absence from the brain. The theory in this form could be easily adapted to the theory that the vaccine virus is the cause if one agreed with Pirquet [153] that the essential process in infection with vaccine virus is an allergic one

151. Aldershoff, H.: Tribuna med. **64**:307, 1930.
152. Glanzman, E.: Schweiz. med. Wchnschr. **57**:145, 1927.
153. Pirquet, C. E.: Arch. Int. Med. **7**:259, 1911.

and that the time necessary for the lesions to show themselves is the time required for the production of antibodies. Certain authors have postulated a less specific and more indefinite allergic process. Keller and Schaefer[154] considered the process one of sensitization to an already present virus. Rivers,[33] on the basis of certain nervous conditions produced in rabbits by the intradermal injection of streptococci and pneumococci and on the basis of the cases of paralysis produced by antirabic treatment, was inclined to give some measure of support to an explanation by allergy, but he did not enter into details as to the possible mechanism of such a process. Of interest in this connection is the case reported from China[155] in which urticaria followed a few minutes after vaccination and encephalitic symptoms occurred in ten days. While the assumption of such a basic allergic reaction to explain the various similar conditions discussed is attractive and with more evidence may prove to be correct, there is at present no evidence requiring the acceptance of such an explanation.

PROPHYLAXIS AND TREATMENT

Since the etiology of postvaccinial encephalitis is still in question, many measures for prevention or treatment must be tentative and of doubtful value. Various suggestions have been made by the committees appointed to study the problem and by independent authors. The following measures have been recommended: the use of only one insertion of lymph at vaccination; the dilution of the lymph used; primary vaccination in early infancy rather than later; the vaccination only of children in perfect health; rest in bed for the vaccinated one while the febrile reaction is present; cessation of vaccination in regions where epidemic nervous disease is present. Doerr suggested that subcutaneous injection of killed virus be tried in place of vaccination by living virus, but the problem of immunization by killed virus is still far from solution and this procedure will probably not be practicable until some means have been found for concentrating the virus. If the condition proves to be due to vaccinial infection of the brain, the fact, noted heretofore, that certain strains of virus produce cerebral lesions in rabbits readily, while other strains do not, may prove to be of importance. In the treatment of patients with postvaccinial encephalitis, it is probably advisable to administer serum from some person recently vaccinated, although proof of the efficacy of this is still lacking.

It is important to emphasize the extremely low incidence of postvaccinial encephalitis, the incidence being especially low in this country. There is no necessity for any cessation of vaccination, since the benefits gained enormously outweigh the possibilities of danger; but cases that occur should be reported, so that all the information possible can be obtained.

SUMMARY

The three most important etiologic theories may be briefly considered again: There is much evidence in favor of the assumption that post-

154. Keller, W., and Schaefer, W.: Jahrb. f. Kinderh. **125**:253, 1929.
155. McClure, W. B.: China M. J. **44**:526, 1930.

vaccinial encephalitis is caused by the direct action of vaccine virus on the brain, but two important objections to this are not yet satisfactorily explained—the lack of vaccine virus in the brain in most cases and the differences between the lesions in man and those produced experimentally in animals. The work of McIntosh may, with further corroboration, remove the second obstacle. The epidemiologic facts apparently opposed to this theory can be explained by the assumption of variations in susceptibility to the encephalitogenic action of the vaccine virus. The theory of an activation of some unknown virus is largely supported as an alternative explanation by those who regard the obstacles to the acceptance of the first explanation as unsurmountable. There is little, if any, positive evidence in favor of this theory which cannot be equally well explained on the basis of the theory that the vaccine virus is the cause. The conception of an allergic reaction as an explanation has no direct evidence in its favor.

Notes and News

University News, Appointments, Promotions, Resignations, Deaths, etc.—In the Rockefeller Institute for Medical Research, Oskar Seifried has been promoted from associate to associate member, and George P. Berry, Elmer E. Fleck, Thomas Francis, Jr., Raymond C. Parker and Robert E. Steiger from assistants to associates.

In the school of medicine of the Creighton University, Omaha, Thomas McCurdy and Clarence Moran have been appointed assistants in pathology; M. W. Barry has resigned as instructor in pathology.

Max Cutler has resigned as director of research and attending radiation therapist in the New York City Cancer Institute to accept the directorship of the tumor clinic of the Michael Reese Hospital in Chicago.

Taichi Kitashimi has been elected director of the Kitasato Institute for Infectious Diseases, Tokio, to succeed the late Shibasaburo Kitasato.

New appointments to the staff of the New York Hospital-Cornell Medical College Association include Eugene L. Opie, now professor in the University of Pennsylvania, as professor of pathology and pathologist to the hospital, and James M. Neill, now professor in Vanderbilt University, as professor of bacteriology and immunology. James Ewing retires from the professorship of pathology at Cornell, which he has filled since 1899, and will devote himself to the study of cancer and to the Memorial Hospital where he is president of the medical board.

Departmental Bibliography in Place of Collected Reprints.—Instead of supplying bound volumes of reprints, as has been the custom, the department of pathology of Columbia University, New York, has prepared a list of the recent publications by its members, reprints of which may be obtained on request.

Recommendations About Postmortem Examinations in New York City.—Recommendations to bring about cooperation between hospital authorities and funeral directors in the matter of postmortem examinations are set forth in the report of a joint committee representing the New York Academy of Medicine, the New York Pathological Society and the Metropolitan Funeral Directors' Association. The committee urges that hospitals avoid unnecessary delays in obtaining permission for necropsies, that they should obtain necessary data for a death certificate when a patient is admitted and that they arrange to inform funeral directors promptly when bodies are ready. The funeral director on his part must recognize the obligation of the hospital to obtain permission from the family of the deceased for examination. He must present to the hospital acceptable written authority from the family to take charge of a body. Other recommendations concern the selection of funeral directors by hospital authorities, reports of death to the medical examiner and the technic of necropsy. It is suggested that an embalmer be present at the examination. Finally, the committee recommends the appointment of a continuing joint committee representing the same organizations with the addition of a representative of the hospital executives. The report was approved by the council of the New York Academy of Medicine.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

STUDIES ON THE "ACID DEFICIT" IN PERNICIOUS ANEMIA. JOSEPH E. CONNERY and NORMAN JOLLIFFE, Am. J. M. Sc. **181**:830, 1931.

A return of free acid in the gastric contents is reported in one patient suffering from pernicious anemia. In eleven cases of pernicious anemia no change in "acid deficit" could be demonstrated following liver treatment over a period of from one to fourteen months.

AUTHORS' SUMMARY.

THE RELATION OF BROCA'S CENTER TO LEFTHANDEDNESS. KARL ROTHSCHILD, Am. J. M. Sc. **182**:116, 1931.

Location of speech center and preference for one side of the body stand in only loose connection. Location of Broca's center in the right hemisphere is compatible with right handedness. Description of two such cases, discovered following apoplectic insults, is herewith presented. In both cases there are left handed and right handed persons in the family. A combination of both "seitigkeitsanlagen" produces true left sidedness.

AUTHOR'S SUMMARY.

FURTHER STUDIES IN A CASE OF CALCIFICATION OF SUBCUTANEOUS TISSUE ("CALCINOSIS UNIVERSALIS") IN A CHILD. W. BAUER, A. MARBLE and G. A. BENNETT, Am. J. M. Sc. **182**:237, 1931.

Further studies in a case of "calcinosis universalis" are reported. Studies of calcium and phosphorus balance indicated a marked tendency to retain the absorbed calcium and phosphorus in spite of normal blood calcium and phosphorus values. This tendency was more marked in the case of calcium than phosphorus. Ammonium chloride acidosis produced an increase in the urinary excretion of calcium and phosphorus. Chemical analysis of a calcareous nodule removed at biopsy showed the presence of a negligible quantity of uric acid, a moderate amount of cholesterol and fatty acids, and calcium and phosphorus in the amount and ratio, one to the other, commonly found in adult bone and pathologic human calcification. Histologic study showed no evidence of antecedent tissue necrosis, nor did it suggest any explanation for the abnormal calcium deposits. The foregoing results suggest that the basis of the disorder lies in an abnormality of calcium and phosphorus metabolism. It is suggested that the increased retention of calcium and phosphorus may be the result of local cellular conditions as yet undetermined.

AUTHORS' SUMMARY.

THE EPITHELIOID CELLS. R. S. CUNNINGHAM and EDNA H. TOMPKINS, Am. Rev. Tuberc. **23**:71, 1931.

It seems that many substances introduced into the subcutaneous connective tissues are capable not only of producing accumulations of large mononuclear cells, but of modifying the morphology and physiology of these cells in different ways. When the material introduced into the tissues interferes with the normal metabolism of the cell it is probable that epithelioid cells are produced. This seems true whether the interference acts from within or without the cells. The authors wish to present their ideas merely as a different approach to cellular physiology and pathology than has previously been possible.

H. J. CORPER.

NUTRITIONAL MUSCULAR DYSTROPHY. M. GOETTSCH and A. M. PAPPENHEIMER, J. Exper. Med. **54**:145, 1931.

A diet is described that leads to a progressive, highly selective, and ultimately fatal dystrophy of the voluntary muscles. Guinea-pigs and rabbits are susceptible, rats resistant. The diet used is complete in known requirements, except for vitamin E; the addition of this factor, however, does not prevent the development of the disease. The lesions are not due to inanition, infection or scurvy, and must be referred to some still unknown factor.

AUTHORS' SUMMARY.

NERVE ENDINGS IN MUSCULAR DYSTROPHY. W. M. ROGERS, A. M. PAPPENHEIMER and M. GOETTSCH, J. Exper. Med. **54**:167, 1931.

The nutritional muscle dystrophy of guinea-pigs and rabbits is primarily a degeneration of the muscle fibers and is not associated with visible alterations of the peripheral nerves or their motor terminals.

AUTHORS' SUMMARY.

EFFECT OF TESTICLE EXTRACT ON RED CELLS. G. FAVILLI, J. Exper. Med. **54**:197, 1931.

Testicle extract possesses a notable power to increase red cell fragility. Testicle extracts of the rat, rabbit and guinea-pig all exhibit this property, which is most pronounced with the extract of the rat and least so with that from the guinea-pig. Splenic extract does not possess the property, or possesses it only to a very slight degree. These results support the hypothesis that the factor in testicle extract that enhances infections (the Reynals factor) does so by altering the permeability of the host tissue.

AUTHOR'S SUMMARY.

PYOCYANINE, AN ACCESSORY RESPIRATORY ENZYME. E. A. H. FRIEDHEIM, J. Exper. Med. **54**:207, 1931.

Pyocyanine, the blue pigment of B. pyocyaneus, can increase the respiration of living cells to a great degree (maximum observed increase twenty-four fold). The reversibility of its oxidation and reduction is responsible for this. The effect is nonspecies-specific and has been observed in varying degrees with B. pyocyaneus, Staphylococcus aureus, Pneumococcus type III and the red blood corpuscles of rabbits. The effect of pyocyanine is dependent on the presence of another respiratory ferment sensitive to potassium cyanide and carbon monoxide. The increase of respiration induced by pyocyanine is paralleled by an increase in the respiratory quotient. The pyocyanine catalysis is not indiscriminately effective in all oxidations, but only in the oxidation of certain substances closely associated with the bacterial body.

AUTHOR'S SUMMARY.

AGE OF LYMPHOCYTES IN PERIPHERAL BLOOD. B. K. WISEMAN, J. Exper. Med. **54**:271, 1931.

The study of blood from rabbits with normal and with hyperactive lymphatic tissue reveals, in the latter, a greater percentage of lymphocytes with heavily basophilic cytoplasm and numerous mitochondria. This indicates that cytoplasmic basophilia and mitochondrial content can serve as criteria of the degree of maturity of the lymphocyte, these characters having the same significance in this relation as obtains with other blood cells. Basophilia is the more evident and reliable indicator of youth of the cells. The classification of lymphocytes into three groups, according to degree of basophilia, has yielded figures that show the proportions of the three to be relatively stable in blood from normal adult human beings and rabbits. Size is not strictly a function of age in lymphocytes. Moreover, there is no correspondence in the size of lymphocytes in supravital films and in fixed

specimens obtained by the "cover glass" method. There is a change of size during fixation. Although lymphocytes of intermediate and large size may be of any age, in supravital preparations the majority are young cells, whereas in fixed films the reverse obtains. The small lymphocyte may be of any age in specimens examined by either technic. The total number of lymphocytes circulating at any given time is not necessarily an index to lymphoid activity.

AUTHOR'S SUMMARY.

MYOCARDIUM IN YELLOW FEVER. WRAY LLOYD, University of Toronto Studies, Pathologic Series, No. 8: University of Toronto Press, 1931.

An attempt at a physiopathologic correlation has been made in a myocardial disease that can be reproduced alone in a healthy animal and made the basis of a laboratory experiment. Attacking the problem in this fashion, an especial effort has been extended to answer two questions proposed for solution, when the problems of the study were first stated. At this time, the need of determining the cause of the bradycardia in yellow fever and of learning the significance and constancy of the degenerative lesions of the myocardium was stressed. A solution to the former is strongly suggested in the degenerative lesion of the sino-atrial node, and an answer to the latter is found in the parallelism of occurrence of the electrocardiographic evidences of altered function with the appearance of degenerations in the auricular muscle, auriculoventricular bundle and ventricle.

AUTHOR'S SUMMARY.

EFFECTS OF HEMORRHAGE ON THE VASCULAR NERVOUS MECHANISM. A. CHAUCHARD, B. CHAUCHARD and D. T. BARRY, Brit. J. Exper. Path. **12**: 190, 1931.

Modifications of the excitability of the parasympathetic inhibitory mechanism of the heart and of the vasomotor mechanism are shown to occur as a result of hemorrhage in dogs. Changes of the rheobasis are not distinctive in value, and this holds for both peripheral and central stimulation of the inhibitory apparatus and for central stimulation of the vasomotor. The chronaxia, on the other hand, is invariably increased by loss of blood for all the reactions tested, and the extent of the increase is roughly proportional to the severity of the hemorrhage. Restoration of the blood lost, after defibrination, causes more or less complete return to former values of excitability. Temporary recovery of these values is also determined by injection of saline solution.

AUTHORS' SUMMARY.

THE CAUSES OF ICTERUS NEONATORUM. K. J. ANSELMINO and F. HOFFMANN, Arch. f. Gynäk. **143**:477, 1931.

The cause of the increased amount of hemoglobin, erythrocytes, glutathione, total blood volume and blood catalase, relative increase in the weight of the heart and rapid pulse in the fetus lies in the condition of lowered oxygen tension under which it lives. The sum of the alterations mentioned is entirely similar to the changes noted both in mountain climbers and in animals kept experimentally under conditions of lowered oxygen tension identical with those of high altitudes. The oxygen tension in the maternal uterine artery averages 14.56 per cent by volume, whereas the oxygen tension in the corresponding fetal umbilical arteries is only 3.53 per cent by volume—about one-fourth that of the maternal blood. The average hemoglobin is 24 Gm. per hundred cubic centimeters (150 per cent) and erythrocyte count 6,500,000 per cubic millimeter. The total blood volume averages 12 per cent of the body weight, an increase of 50 per cent above normal. In the acclimatization of the new-born infant to the conditions of atmospheric air the hemoglobin rapidly undergoes decomposition and bilirubin in the blood plasma rapidly rises for several days after birth, just as it does in animals experimentally acclimatized to conditions of high altitude and suddenly reacclimatized

to oxygen tension at normal altitude. This unusually high bilirubin content of the plasma offers a part of the explanation of the occurrence of icterus. However, it fails to explain why icterus does not occur in about 20 per cent of the new-born infants.

A second factor, that of variability in the permeability of the cutaneous capillaries, is very important. Localized icterus can be produced in nearly all newborn infants by the cataphoretic introduction of histamine into the skin. The increased permeability of the capillaries so produced causes the visible appearance of icterus in the area of skin treated.

LAWRENCE PARSONS.

ON THE ORIGIN OF HYPOPHYSEAL CACHEXIA (SIMMOND'S DISEASE). W. MERZ, Frankfurt. Ztschr. f. Path. **40**:452, 1930.

Two cases are reported. The first case was that of a 35 year old man who showed progressive loss of weight, gastric distress, alimentary glycosuria, decreased basal metabolism, increasing weakness and neurasthenia. These symptoms were manifest for seventeen years and were first noticed shortly after an attack of angina. At autopsy, a colloid cyst of the size of a pea was found in the midportion of the hypophysis. The cyst had led to a diminution of the size of the anterior lobe and, to a less degree, of the posterior lobe. Histologically, there was a decrease of all the elements of the anterior lobe, but especially in the number of eosinophilic cells. In the region of the infundibulum, a marked sclerosis and atrophy was found. The thyroid revealed atrophic changes. The diagnosis of hypophyseal cachexia was made even though a few typical symptoms, such as atrophy of the genitalia and loss of hair, were not present. The author suggests that a toxin following angina rather than the colloid cyst had led to the changes of the anterior lobe of the hypophysis and to the hypophyseal cachexia. The second case was that of a 44 year old woman. Her first clinical symptoms were characteristic of exophthalmic goiter. Both superior thyroid arteries were ligated. Two months after the operation, she started to lose weight and developed a cachexia which became progressively worse. There were no changes in the carbohydrate metabolism. The autopsy revealed a marked atrophy of the hypophysis which weighed 0.4 Gm., pseudocirrhosis and atrophy of the liver, cortical contraction of the suprarenals, atrophy of the ovaries and mammary glands and a colloid goiter with hyperplasia. The crines pubis were markedly reduced. The anterior lobe of the hypophysis histologically showed a marked sclerosis and actual scar tissue. In several places, foci of lymphocytic infiltrations were found. The eosinophilic cells were reduced in number. The author's opinion is that a cytotoxin appeared following exophthalmic goiter, which produced the changes in the hypophysis, suprarenals, ovaries and liver. The case presents a combination of exophthalmic goiter and hypophyseal cachexia which, as the author states, is not known in the literature.

O. SAPHIR.

GENETICS AND PATHOLOGY. S. G. LEWIT, Frankfurt. Ztschr. f. Path. **40**:552, 1930.

This article deals with the etiology and differentiation of diseases biologically. Much weight is put on heredity. The individual variation of the same disease is discussed from various angles. An attempt is made to explain a number of diseases by a certain constitution (genotype) which is not apparent until external influences make this constitution manifest in the form of a disease. Tuberculosis is an example of this type. Another group of diseases is caused entirely by the genotype of the individual and does not need external influences to become manifest. Hemophilia is an example of such a disease. The third group embraces diseases that are produced primarily by external causes, as are most infectious diseases. This type of disease is referred to as paratypic.

O. SAPHIR.

THE INFLUENCE OF THE FEMALE SEX HORMONE AND THE ANTERIOR HYPOPHYSEAL HORMONE ON THE STRUCTURE OF THE HYPOPHYSIS. B. ZONDEK and W. BERBLINGER, Klin. Wchnschr. **10**:1061, 1931.

The morphologic changes caused in the anterior lobe of the hypophysis of the rat and mouse by castration are not modified by the prolonged use of the female sex hormone. A single dose of the follicle-ripening hormone of the anterior lobe of the hypophysis stimulates certain maturation changes in that lobe in the young animal. Repeated doses of the follicle-ripening and luteinization hormone cause a definite maturation of the anterior lobe.

AUTHORS' SUMMARY.

PLETHORA. L. ASCHOFF, Verhandl. d. deutsch. path. Gesellsch. **25**:106, 1930.

Volumetric studies of the blood from the heart and thoracic aorta in a hundred autopsies disclosed an increased volume in the following conditions in order of importance: essential hypertension with hypertrophic heart and without arteriosclerosis, arteriosclerosis, obliteration of the pleural cavities, primary contracted kidneys with hypertrophic heart, right-sided cardiac hypertrophy and its related causes, toxic goiter and frank valvular lesions. The smallest volume were found in acute effusions into the abdominal cavities, fatal peritonitis, sepsis with marked perspiration and evaporation, cachexia of carcinoma, and hypertension with secondary contracted kidneys. Blood volume increases more rapidly than heart weight, in the ratio of 2:3.5. Edema, state of coagulation or its lack, regional distribution has no direct effect on blood volume. The increase in blood volume might be interpreted as an expression of disturbed circulatory mechanism possibly due to chemical disturbances. In heart failure from varying causes it might be explained as a compensatory process to fill vessels otherwise not distended. The increase of blood volume in essential hypertension is not explained.

SOL ROY ROSENTHAL.

THE GENERALIZED CHANGES IN INFLAMMATION. B. FISCHER-WASELS, Verhandl. d. deutsch. path. Gesellsch. **25**:115, 1930.

The injection of kieselguhr subcutaneously into mice and rabbits called forth a granulomatous and a necrotic reaction with suppuration. The generalized reaction resulting from reabsorption of protein-split products was as follows: anatomically, by a rounding of the reticulo-endothelial cells of the liver and spleen with swelling of the nuclei and basophilic staining of the cytoplasm; functionally, by their mobilization as seen by an increased absorption of trypan blue and casein, and metabolically, by the increased oxygen consumption. In granulomatous lesions, the oxygen consumption is slight as compared to the necrotic suppurative lesions. After evacuation of the pus in the necrotic lesions the oxygen metabolism returns to normal.

SOL ROY ROSENTHAL.

ORGAN METABOLISM BY TISSUE ACTIVITY AND ANAPHYLAXIS. W. BÜNGELER, Verhandl. d. deutsch. path. Gesellsch. **25**:125, 1930.

Intravenous injections of casein and horse serum into white rats and subsequent determinations of oxygen metabolism of liver, spleen, kidneys and lungs by Warburg's gasometric methods gave the following results: (*a*) In animals killed immediately after injection, small injections increase and large injections decrease the oxygen metabolism during the early stages (first five hours); later there is a constant rise which lasts twenty-four hours and is followed by return to normal. (*b*) During the early stages of phagocytosis of acid dyes, increased oxygen consumption was found in the liver, kidneys and other organs, but after phagocytosis is completed organ metabolism is again normal. (*c*) Intravenous injection of india ink and immediate killing of the animal with subsequent deter-

mination of metabolism showed that only when phagocytosis had ceased did oxygen metabolism return to normal, and then only slowly. (*d*) Guinea-pigs, white mice and rabbits killed during typical anaphylactic shock showed marked decrease of oxygen metabolism. In animals not sufficiently prepared or sufficiently prepared but not sensitized, there was marked increase in oxygen metabolism, especially in the liver and spleen.

SOL ROY ROSENTHAL.

PHAGOCYTOSIS OF COLLOID BODIES IN LIVING BODY AND IN TISSUE CULTURES. J. TANNENBERG, Verhandl. d. deutsch. path. Gesellsch. **25**:128, 1930.

The author seeks to prove that phagocytosis is not wholly dependent on the increase of particles brought to the cell by the circulation or by the surface area of the cells. That there is an increase of phagocytosis by a slowing of the circulation, the author shows by his injections of india ink, but the injection of trypan blue (which is held in fine colloid suspension), macrophages, histiocytes and fibroblasts all having equal exposure to the dye results in a greater phagocytosis by the macrophages than by either fibroblasts or histiocytes. This he interprets as a difference in function, dependent on the structure of the cell, which much be considered as a potent factor in phagocytosis.

SOL ROY ROSENTHAL.

THE PATHOGENESIS OF IRRADIATED CHOLESTEROL POISONING. G. SCHRETTER and L. HASLHOFER, Ztschr. f. d. ges. exper. Med. **76**:352, 1931.

When large doses of irradiated cholesterol were given to dogs over a long enough period of time, the nitrogenous residuum in the blood became markedly increased. No lesions were found in the glomerular tufts of the kidneys. The suprarenals, liver and brain showed no changes sufficient to produce the high blood nitrogen. Therefore, it is suggested that the disturbance may be metabolic in origin.

PEARL ZEEK.

THE RÔLE OF THE SPLEEN IN METABOLISM. S. G. STSCHEDROWITZKY and S. A. SELTZER, Ztschr. f. d. ges. exper. Med. **76**:369, 1931.

Splenectomy in dogs was followed by a slight increase in thyroid function, increased alkali reserve in the blood, decreased blood sugar, increased blood cholesterol, increased blood calcium and lymphocytosis. Both normal and splenectomized dogs showed a decrease in blood calcium following the ingestion of spleen. Similar feeding caused no change in blood sugar or cholesterol in normal animals, but in splenectomized dogs the blood sugar was raised and the cholesterol lowered. It is suggested that the spleen may produce a hormone and may be closely related to glands of internal secretion.

PEARL ZEEK.

EXPERIMENTAL LEUKOSIS IN THE FOWL. O. THOMSEN and J. ENGELBERTH-HOLM, Acta path. et microbiol. Scandinav. **8**:121, 1931.

The paper describes and discusses the results obtained in an effort to produce leukosis in the fowl by injections of tar emulsion into the bone marrow. A form of tar was used that had been found to produce carcinoma of the skin in mice. Of sixty-two chickens in which tar was injected into the bone marrow every fifth day, nine developed extensive myeloid hyperplasia in various organs and tissues, which resembled closely the changes observed in spontaneous myeloid leukosis in the fowl. In some of the animals there was an increase in the leukocytes in the blood. Repeated intravenous injections of tar emulsion over a period of several months have not had any effect.

Pathologic Anatomy

ANOMALY OF THE BILIARY TRACT. ANTONIO GENTILE, Am. J. M. Sc. **182**:95, 1931.

A case is reported of communicating ducts between the hepatic and cystic ducts, separate entrances of the common and hepatic ducts into the duodenum and an occlusion of the common duct. It is presented as a probably unique congenital anomaly of the biliary tract. An attempt is made to explain the embryologic mechanism underlying this anomaly.

AUTHOR'S SUMMARY.

INTRAHEPATIC LITHIASIS. HARRY KOSTER and I. E. GERBER, Am. J. M. Sc. **182**:99, 1931.

A case of intrahepatic lithiasis is presented with unusually large stones. A striking feature of this case is the freedom from symptoms during the long period in which the development of the stone undoubtedly occurred. A discussion of the causes and associated features of the development of stone is presented.

AUTHORS' SUMMARY.

A PERSISTENT OSTIUM ATRIOVENTRICULARE COMMUNE WITH SEPTAL DEFECTS IN A MONGOLIAN IDIOT. G. M. ROBSON, Am. J. Path. **7**:229, 1931.

A case is reported in which a persistent ostium atrioventriculare commune is associated with a defect in the base of the interventricular septum and a persistent ostium primum. This occurred in the heart of a Mongolian idiot who showed also a complete absence of true ovarian tissue. The cardiac defect is believed to be due to faulty development of the endocardial cushions. Four of the nine similar cases found reported in the literature occurred in Mongolian idiots.

AUTHOR'S SUMMARY.

THE SPECIFIC CHARACTER OF TOXIC CIRRHOSIS IN CINCHOPHEN POISONING. D. C. BEAVER and H. E. ROBERTSON, Am. J. Path. **7**:237, 1931.

Preparations of cinchophen have been shown definitely to be toxic for certain persons. The toxic effects are directed most severely and specifically against the liver. Unknown factors, apparently independent of the quantity of the drug used, appear to be significant in creating a predisposition or idiosyncrasy for the drug. Various grades and stages of hepatic degeneration have been described. These are presumably dependent on the completeness and rapidity of the initial reaction. The reaction may be rapid and complete, with the induction of acute atrophy of the liver, or slower and less complete, with apparent recovery. Intermediate between these two extremes subacute forms of intoxication may ensue and may become manifest both clinically and pathologically as a type of hepatic atrophy or cirrhosis, which corresponds in its anatomic characteristics to the distinctive toxic cirrhosis as described by Mallory. The clinical and anatomic characteristics of toxic cirrhosis appear to be specific and essentially dissimilar to the ordinary Laënnec or portal type. The clinical data and correlated studies of pathologic anatomy in five cases of intoxication from cinchophen constitute the basis for this study.

AUTHORS' SUMMARY.

GRANULOMATOUS ABSCESS OF THE LIVER OF PYOGENIC ORIGIN. D. C. BEAVER, Am. J. Path. **7**:259, 1931.

Abscesses of the liver, originating from within the field of drainage of the portal vein, form a significant clinical and pathologic group. They usually take origin from primary intestinal foci through the production of local thrombo-

phlebitis. The hepatic suppuration develops from the passage of infected emboli from the primary foci by way of the portal circulation to the liver. The primary thrombophlebitis may induce thrombosis of the portal vein and pylephlebitis, or this feature of the lesion may be absent. As the cases emphasize, the primary focus may be cryptogenic. From the appearance of the abscess, however, the source may be suspected. A characteristic distribution and type of abscess are produced by each method of hepatic dissemination. The abscesses of portal origin are at first multilocular, owing to the multiple foci in emboli. Each multilocular abscess usually remains discrete, although it may be multiple. Involvement of the right lobe alone is most common. General hepatic dissemination, in this type, is unusual. The significance of the pyogenic cocci as etiologic agents has been emphasized. The illness associated with abscess of the liver may be extremely insidious, and as the primary focus may be cryptogenic, so also the hepatic lesion itself may exhibit this same characteristic. Progression into extreme chronicity may occur, with preservation of the original multilocular arrangement, or a solitary, adequately encapsulated abscess may result. In the cases of extreme chronicity a granulomatous reaction has been found, with the pyogenic cocci demonstrable as the etiologic agents. Such cases resemble the granulomas of actinomycosis in their chronicity and in their granulomatous characteristics. Eight cases representative of pyogenic abscesses, possessing granulomatous changes in various stages of their evolution, have been presented.

AUTHOR'S SUMMARY.

ERYTHROBLASTOSIS WITH JAUNDICE AND EDEMA IN THE NEWLY BORN. J. A. FERGUSON, Am. J. Path. **7**:277, 1931.

In the six cases reported, in all of which the patients died during birth or shortly after, a detailed description of the pathologic changes has been given. The outstanding feature was the occurrence of abnormal extramedullary hematopoietic activity in full term nonsyphilitic infants. In each instance there was a persistence of the fetal mode and location of blood-forming activity without a corresponding retardation in general embryologic development. Three cases showed marked jaundice at birth. In one of these, bile stasis was present in the liver. This may have been due to excessive hemolysis of large numbers of imperfectly differentiated erythrocytes loading the liver cells with bile pigment more rapidly than it could be taken care of by the bile-excreting apparatus. One of the three cases showing jaundice was complicated by an infection, but this was not thought to be related to abnormal hematopoietic activity or to the jaundice. Two cases showed marked edema at birth, which corresponded to the condition known as hydrops congenitus. One case showed neither jaundice nor edema. All cases showed a marked enlargement of the spleen and liver. The features which these cases have in common with well known disease conditions of infancy have been discussed. A few factors that are thought to be of etiologic significance have been mentioned. However, the cause is still unknown. The cases described in this report, when considered as a group, are probably representative of a definite disease entity of the newly born, and whatever the etiology may be, the underlying cause is undoubtedly the same in each instance, whether or not the individual case is characterized by jaundice or edema, or whether both jaundice and edema are lacking. The term erythroblastosis in the newly born is applied to the pathologic syndrome described in the six cases reported here because it best depicts the anatomic changes.

AUTHOR'S SUMMARY.

STREPTOCOCCUS HEPATITIS. H. E. MACMAHON and F. B. MALLORY, Am. J. Path. **7**:299, 1931.

The more common inflammatory changes in the liver in cases of streptococcus infection with and without septicemia are described. Emphasis is laid on a less common lesion, of which three cases are given in detail. This is characterized by

focal or diffuse areas of liver tissue showing necrobiotic changes and necrosis, infiltrated with an inflammatory exudate. A Gram-Weigert stain shows streptococci in large numbers in the lesions of two of these livers. The similarity of this lesion to the histologic picture at times encountered in acute yellow atrophy is discussed, and the suggestion is made that a careful bacteriologic search of the liver in the fixed preparation together with a culture of the liver at the time of the autopsy might reveal bacteria within the lesions more commonly than is suspected—particularly in those cases of so-called acute yellow atrophy showing a very irregular distribution of the lesion—a condition that is extremely difficult to explain purely on the basis of a circulating toxin in the blood. Another case is described with a chronic inflammatory reaction within the liver, showing on the one hand degeneration, necrosis, exudation and bacteria, and on the other a very active proliferation of bile ducts and connective tissue. This case is presented more for discussion than as a proved case of chronic progressive cirrhosis of infectious origin. The last point that is considered is the histologic and gross changes that one may find in the healed stage of these acute and chronic inflammatory lesions. The second part of the paper is devoted to the results of experimental work. A streptococcus obtained from an early case of scarlet fever was injected free from toxin into one of the radicals of the portal veins of both guinea-pigs and rabbits. The animals were killed at varying intervals, and the lesions produced, together with the results of bacteriologic studies, are fully described and compared with the lesions seen in cases in human beings.

AUTHORS' SUMMARY.

PULMONARY ASBESTOSIS. WILLARD B. SOPER, Am. Rev. Tuberc. **22**:571, 1930.

A case of typical asbestosis is reported. The most common single symptom of pulmonary asbestosis is dyspnea. This and the other symptoms are essentially those of a generalized progressive fibrosis of the lungs. The physical signs are substantially those of generalized fibrosis of both lungs and basal pleurisy. Asbestos contains but a small amount of free silica, but probably conduces to a more hasty evolution of any accompanying tuberculosis as in the better understood forms of silicosis. An immediate diagnosis at autopsy is made possible by simply squeezing out a drop of juice from the lung when the asbestosis bodies in large numbers are readily visible under the microscope.

H. J. CORPER.

ENCEPHALITIC, IDIOPATHIC AND ARTERIOSCLEROTIC PARKINSONISM: A CLINICOPATHOLOGIC STUDY. MOSES KESCHNER and PAUL SLOANE, Arch. Neurol. & Psychiat. **25**:1011, 1931.

Anatomic observations are contrasted in seven cases of parkinsonism that were observed clinically for about seven years. Three of the cases were diagnosed as chronic encephalitic parkinsonism, two as idiopathic or genuine Parkinson's disease and two as arteriosclerotic parkinsonism. The changes in the three types were most frequent and marked in the substantia nigra and globus pallidus (the pallidonigral system); the locus caeruleus was practically as frequently involved as the substantia nigra. The pallidum seemed to have been affected mostly in the idiopathic cases. The cerebellum was intact, while other basal formations (the putamen, optic thalamus, red nucleus and hypothalamus) were involved in the three types. The changes in the encephaltic type were both degenerative and inflammatory; the latter, however, may be quite mild, when the case may resemble the genuine type of parkinsonism. In these cases inflammatory perivascular infiltrations were absent. The arteriosclerotic form could be suspected from the condition of the arteries. The anatomic changes are not characteristic enough to permit of a differential diagnosis between the three types. In all of them the process is diffuse and is hardly ever localized. For this reason it is not possible to correlate the anatomic observations with the clinical picture.

GEORGE B. HASSIN.

THE ORIGIN AND FORMATION OF SENILE PLAQUES. ARMANDO FERRARO, Arch. Neurol. & Psychiat. **25**:1042, 1931.

Ferraro found that the senile plaques originate from nerve cells, oligodendroglia (the glia nuclei of Nissl) and especially microglia cells. In rare instances fat granule bodies are found in them. The oligodendroglia and microglia undergo disintegration, with the formation of a granular amorphous substance. This constitutes the argyrophile substance of the plaque, thus contributing to the increase in size of the plaques. Surrounding the plaques, usually at some distance, are numerous astrocytes, mainly as a reaction. Sometimes they form a part of the plaque, when they degenerate and thus also contribute to the increase in size of the plaque. The axis cylinders of a plaque are broken up. Ferraro believes that oligodendroglia and microglia cells may undergo some particular changes and constitute a small plaque.

More numerous are the plaques developing from microglia cells. Minute plaques may also originate from transformed nerve cells. From the various single elements forming small plaques, larger plaques form either by fusion of the former or by degeneration of oligodendroglia and microglia. Nerve fibers never give origin to senile plaques, but contribute to their growth through a process of fragmentation and gradual disintegration of the neurofibrils.

GEORGE B. HASSIN.

ENCEPHALITIS PERIAXIALIS DIFFUSA (SCHILDER'S DISEASE). C. DAVISON and W. SCHICK, Arch. Neurol. & Psychiat. **25**:1063, 1931.

A detailed clinical and pathologic report of Schilder's disease is given because of the unusual features: marked signs of extrapyramidal disorder and bilateral optic atrophy. The striking pathologic features were the bilaterality of the process, which extended from the frontal to the occipital lobe, and involvement of the corpus callosum, optic nerves, ependyma and basal ganglions. The changes were mainly degenerative, probably due to a toxin. The authors offer to call Schilder's disease encephalopathia periaxialis diffusa.

GEORGE B. HASSIN.

THE NERVOUS LESIONS OF SUBACUTE OR CHRONIC EXPERIMENTAL POLIOMYELITIS. BETTINA WARBURG, Arch. Neurol. & Psychiat. **25**:1191, 1931.

Fifteen rhesus monkeys infected with poliomyelitis were kept alive for from nineteen to thirty days after the onset of symptoms, and the spinal cord, medulla, basal ganglions, cortex and cerebellum were studied. Regardless of the mode of infection, the severest lesions were in the lumbar cord; meningitis was not a prominent feature; the blood vessels of the anterior horns were more infiltrated with lymphocytes and polymorphonuclears than elsewhere. The tissues were also infiltrated, especially in areas of severe parenchymatous destruction. Here the infiltrating cells were lymphocytes and microglia cells. The fibrous and protoplasmic astrocytes were also in evidence, but oligodendroglia cells were practically absent. Fewer anterior horn cells survived in the lumbar than in the cervical region, and in the earlier stages satellitosis was more common than neuronophagia, which was a prominent feature in the later stages.

Neuronal destruction was present mainly in the anterior horns; it was mild in Clarke's columns, in the lateral and posterior horns and in the medulla, pons, midbrain (inciuding the substantia nigra and red nucleus) and basal ganglions. The corpus striatum was practically intact. The meninges over the cortex were more involved than over the spinal cord, while parenchymatous cortical changes were present in the anterior, frontal, precentral and posterior central areas. No relationship was noted between the extent of the perivascular infiltrations and the degenerative changes which progressively decreased cephalad. In the medulla the sensory nuclei were also involved, and in four animals that made good functional recoveries inflammatory changes persisted in the central nervous system.

GEORGE B. HASSIN.

DEATH IN ASTHMA, WITH AUTOPSY. A. M. FISHER and J. P. BECK, J. Allergy **2**:149, 1931.

A man, aged 32, died during an acute attack of asthma. Air had escaped into the chest cavities through small ruptures of the emphysematous lungs, which were not collapsed. The bronchioles were narrow and plugged with thick mucus containing eosinophils and Curschmann's spirals; the mucosa was thrown into folds; the basement membrane was thick and hyaline; the muscular wall was hypertrophied, and all the layers were infiltrated with plasma cells and eosinophils. The right side of the heart was hypertrophied.

ROENTGENOGRAMS IN THE STUDY OF INTRACRANIAL HEMORRHAGE IN THE NEWBORN. F. M. B. ALLEN and H. I. MCCLURE, Arch. Dis. Childhood **6**:97, 1931.

Intracranial hemorrhages in the new-born may be studied with advantage by stereoscopic roentgen examination after the injection of a contrast medium ("röntyum") into the carotid artery.

THE RELATION OF THE NERVOUS SYSTEM TO A PATCHY ISCHAEMIA (BIER'S SPOTS) IN ANIMALS. H. P. GILDING, Brit. J. Exper. Path. **12**:66, 1931.

The patchy ischemia observed after hemorrhage occurs in the absence of vasomotor control of the minute vessels concerned. The compensatory vasoconstriction that occurs after hemorrhage is a predisposing cause of the intense local ischemia observed. The production of ischemic patching in animals in denervated areas is in agreement with observations on Bier's spots in man. AUTHOR'S SUMMARY.

THE REPAIR IN VITRO OF EMBRYONIC SKELETAL RUDIMENTS AFTER EXPERIMENTAL INJURY. J. S. F. NIVEN, J. Path. & Bact. **34**:307, 1931.

The rudimentary bony structures of the fowl and the mouse embryo were studied on cultivation in vitro after they had been fractured or incised. The results of the reparative process, which varied according to the period of embryonic life at which the injury was made, are described.

MITOCHONDRIAL CHANGES IN OXALATE AND URANIUM NEPHRITIS. J. GOUGH, J. Path. & Bact. **34**:423, 1931.

In experimental oxalate and uranium nephritis in rabbits, the mitochondria are the first of the cell constituents to show alteration from the normal. Mitochondrial changes are of value in the determination of the time of onset of cellular reaction to injury. Granulation and fusion of mitochondria in the renal epithelium do not necessarily signify a permanent damage. AUTHOR'S SUMMARY.

THE MORBID ANATOMY OF MALIGNANT DISEASE OF THE MEDIASTINAL GLANDS, LUNGS AND PLEURAE. S. ROODHOUSE GLOYNE, Tubercle **12**:54, 1930.

Experience in the postmortem room indicates that malignant growths of the lungs, pleurae and mediastinal glands are more common now than formerly. Furthermore, there is some evidence that a change in type has occurred of late years. In postmortem examinations carried out at Victoria Park twenty years ago, the growths most commonly encountered were those situated in the mediastinal glands; now the type affecting the lungs, with secondary and often slight extension to the glands, has come much more into the picture. The histologic picture shows wide variation; growths vary from undifferentiated small round cell tumors to differentiated columnar mucous-secreting and squamous cell growths, while between the two extremes are growths of large polygonal and spheroidal cells, the so-called medullary growths. Probably nearly all are true carcinomas. The picture pro-

duced by tumors of the mediastinal glands may be summed up as one of compression, displacement, invasion and perforation of the surrounding vital structures. The malignant disease of the bronchi includes single nodular growths and diffuse bronchial carcinomatosis, while the malignant disease of the lung consists of: (1) growths of the lower lobe, generally occupying the whole lobe and producing a completely solid lobe in which the lung tissue is entirely replaced and the bronchi are occluded with growth; cavitation may follow; (2) the growths in the upper lobe resemble those in the lower lobe but are more liable to form cavities and have a predilection for infection of the tracheobronchial glands; (3) growths of the whole lung resemble those of the lower lobe, but completely obliterate interlobar fissures, fill the bronchi, are less liable to cavity formation, and exert pressure on the pulmonary vessels; (4) multiple nodules in the lung, occurring as discrete, yellowish nodules in one or more lobes of the lung; the reason for placing these in a separate class is that they suggest secondary nodules, but a primary growth is difficult to locate, and when small they are liable to be confused with actinomycosis of the lung or lymphadenomatous deposits; (5) the sclerotic type. The fifth type is described in the literature, but the author has not met a true primary, sclerotic, malignant condition of the lung. Primary malignant growths of the pleura are rare, and in all forms pleural effusion is common. The commonest concealed growths are those of diffuse bronchial carcinomatosis, the condition being obscured by bronchiectasis and general sepsis. The association of two totally different morbid conditions in one and the same lung is more common than is generally supposed. Complications of new growths of the lung are generally due to sepsis, the commonest being bronchiectasis; next in frequency is pulmonary abscess, generally in the peripheral part of the lung and usually basal. Gangrene of the lung is less common. Direct extension to the heart is an important complication of all malignant growths of the lung. No organ is immune from a secondary deposit.

H. J. Corper.

Congenital Obliteration of the Larger Bile Ducts. H. Coburg, Frankfurt. Ztschr. f. Path. **40**:281, 1930.

The case of a boy, aged 7 months, who was jaundiced since birth, is reported. At autopsy and subsequent histologic examination, it was found that the ductus choledochus was obliterated. There was no communication between the stump of the duct and the papilla of Vater, which was normal. Parts of the common hepatic and cystic ducts were obliterated. The right and the left hepatic ducts showed marked inflammatory changes. Both were filled with bile. The gallbladder was markedly diminished in size, contained no bile and revealed an inflammatory reaction throughout its wall. The liver was the seat of a typical biliary cirrhosis. The author reviews the various theories explaining such a condition; however, he arrives at no definite conclusions.

O. Saphir.

Calcification of the Vasa Deferentia and the Ampullae. W. Schellenberg, Frankfurt. Ztschr. f. Path. **40**:298, 1930.

A case of calcification of the vasa deferentia and the ampullae is described in a man, aged 48. The etiology of this condition is obscure. Senile changes, tuberculosis, gonorrhea, etc., could be ruled out as etiologic factors. Repeated roentgen examinations of this region, which were done for other reasons, did not disclose the calcification. The changes were found incidentally at autopsy.

O. Saphir.

Lipoid Deposits in the Aortas of Infants. N. Kube and A. Ssolowjew, Frankfurt. Ztschr. f. Path. **40**:302, 1930.

The aortas of 114 infants were examined and stained with sudan III. None of the infants was older than 6 months. In seventy-two of the cases, lipoid deposits were found in the aorta. In one instance they were found in a stillborn infant.

They also were present in an infant 1 day old, and also in two others, 3½ and 9 days old, respectively. The most common locations of the lipoid deposits were as follows: the upper margin of the sinus of Valsalva, the region of the commissure between the right and the posterior cusp of the aortic valve, a portion just above the left part of the sinus of Valsalva, the vicinity of the opening of the ductus arteriosus, the region where the large vessels come off from the arch of the aorta, the intima surrounding the openings of the intercostal arteries and the posterior wall of the aorta. Histologically, a varying amount of lipoid droplets was seen along the elastic lamellae. The intima revealed an accumulation of macrophages, which in some instances were transformed into xanthoma cells. The belief is expressed that the lipoid deposit is a purely infiltrative process, possibly the result of an imperfect lipoid metabolism. There was no demonstrable relationship between acute or chronic diseases and the presence of the lipoid deposits. With increasing age, these deposits not only were found more frequently, but were more severe.

O. SAPHIR.

THE FORMATION OF GIANT FOLDS IN THE MUCOSA OF THE STOMACH. H. J. SCHERER, Frankfurt. Ztschr. f. Path. **40**:357, 1930.

Four cases of formation of giant folds in a circumscribed area of the gastric mucosa are described. The folds were located in the posterior wall of the stomach, close to the larger curvature. There were no clinical symptoms referable to these folds. In one case, the x-ray picture led to the erroneous diagnosis of carcinoma of the stomach. Histologic examination revealed a pure hyperplasia of the mucosa. Moderate inflammatory changes, however, were encountered in two cases. The author believes that the formation of these giant folds was the result of a congenital anomaly, especially because two of the four cases also revealed other congenital anomalies. According to the author's opinion, there are no other similar cases on record. The circumscribed giant folds are thought to represent a "vitium primae formationis" in the sense of an increased "resonance" of certain cells to growth-producing irritations of various kinds, such as the influence of hormones, of nervous irritations, of inflammations and of hyperemia. It could not be determined what specific influences had caused the formation of the giant folds of the gastric mucosa in these four cases.

O. SAPHIR.

A CASE OF A RETRORECTAL LIPOMA. M. A. KOSLOW, Frankfurt. Ztschr. f. Path. **40**:382, 1930.

The presence of a retrorectal tumor is reported in a woman, aged 47. The tumor extended to both sides of the rectum and measured 3 by 3.5 by 12 cm. It had led to a constriction of the lumen of the rectum. Histologically, the tumor consisted of fat cells. The clinical diagnosis was rectal fissure and carcinoma of the rectum. The author suggests that in every case of stricture of the rectum one should think of a retrorectal tumor, especially lipoma.

O. SAPHIR.

DIFFUSE MYELOMA WITH AMYLOID MASSES. E. FREUND, Frankfurt. Ztschr. f. Path. **40**:400, 1930.

The diffuse myeloma is characterized by the absence of circumscribed nodules and by its somewhat slight osteoclastic effect. Such a tumor is described in a woman 72 years of age. The diagnosis was missed grossly, but could easily be made microscopically because of the presence of myeloma cells. Even though there was no generalized amyloidosis, amyloid masses in addition to the myeloma were found in many places, especially in the sternum and vertebrae. These masses were recognized grossly, and the impression was gained that this was a case of amyloid accumulations in healthy bones. Because of their marked calcification, the masses could be detected by the x-rays. The amyloid in many places was phago-

cytosed by giant cells. Its absence in portions gave the mass a peculiar raylike structure. Amyloid growths, contrary to diffuse myelomas, have an osteoclastic effect on the bone. The myeloma and the amyloid accumulations in this case had perforated the cortical portions of bones and the periosteum, and had invaded the adjacent cartilage and connective and fat tissue. The invasion of the periosteal region of the sixth thoracic vertebra led to a fracture of this vertebra and subsequent transverse myelitis.

O. SAPHIR.

MYXOMA OF THE HEART. A. A. WASSILIEFF, Frankfurt. Ztschr. f. Path. **40**:424, 1930.

Two cases of myxoma of the heart are reported. In the first case the heart showed in the region of the left auricle a gelatin-like, pinkish, papillomatous mass, filling the entire left auricle. For the most part, the mass was attached to the auricular wall. The leaflets of the mitral valve were fibrosed. Histologically, the mass showed a large amount of mucin, many small vessels and elastic and collagenous fibers. The author believes that this mass is a tumor, a myxoma, rather than a primary organized thrombus. In the second case the heart revealed a nodule somewhat smaller than a walnut, which was attached to the posterior wall of the left auricle. The surface of the nodule was smooth. It showed several yellow and red areas. The mitral valve was the seat of an acute verrucous endocarditis superimposed on a healed endocarditis. Microscopically, the nodule showed areas of hyalinization and calcification, many vascular spaces lined by endothelial cells and some iron-containing pigment. No mucin or fibrin was present. This nodule was diagnosed as an organized thrombus.

O. SAPHIR.

Pathologic Chemistry and Physics

LACTIC ACID IN THE BLOOD IN CHILDREN. JEROME S. LEOPOLD and ADOLPH BERNHARD, Am. J. Dis. Child. **41**:758, 1931.

The concentration of lactic acid in the blood of twenty-three normal children varied between 9 and 18 mg. per hundred cubic centimeters of blood, the average being 14.8 mg. There was an increase of lactic acid in the blood obtained by application of a tourniquet. In forty-two children ill with various diseases (whose blood was obtained with and without tourniquets) the increase in lactic acid was from 0.2 to 6.8 mg., the average being 3.1 mg. In the blood of the normal children the average variation was 2.1 mg. A definite rise in the lactic acid content of the blood was found in cases of pneumonia with fever. In the convalescent cases without fever the values were considerably lower, but not within the normal range. In cases of rheumatic fever with cardiac involvement there was found an increase of lactic acid. Patients ill with chorea also showed an increased concentration of lactic acid in the blood. There was no relationship between the concentration of lactic acid in the blood and the blood sugar. There seems to be no quantitative relation between the concentration of lactic acid and the carbon dioxide-combining power of the blood.

AUTHORS' SUMMARY.

CHOLESTEROL AND EDEMA. JOSEPH K. CALVIN and A. H. GOLDBERG, Am. J. Dis. Child. **41**:1066, 1931.

The conclusions that may be drawn from a review of the literature and our experimental observations are: The blood cholesterol level in the nephrotic syndrome is practically always considerably elevated above normal, and probably does not return to normal for years, even though edema may be absent for long periods. Although the cholesterol remains above normal even during edema-free periods, it has a tendency to rise and fall with the increase and decrease of edema. Exceptions to this are not uncommon, however, and edema may appear and dis-

appear irrespective of the height of the cholesterol. The appearance or disappearance of the edema, which is usually relatively rapid when it begins, precedes the changes in the cholesterol. The cholesterol possibly may be mobilized from and at the expense of the deposits of fat in the body, for the patients are usually greatly emaciated, which becomes apparent as the edema disappears, even though the blood cholesterol remains relatively high and the intake of food is ample. The cholesterol in the nephrotic syndrome has difficulty in passing from the blood to the tissues, as the ascitic fluid has a very low cholesterol content. The blood cholesterol in the nephrotic syndrome can readily pass through the kidneys into the urine, although the hypercholesteremia antedates by a considerable period the lipoiduria (Murphy). The diet has no influence on hypercholesteremia. The output of cholesterol in the bile is diminished in the nephrotic syndrome, so that apparently a real retention in the blood exists (Herrnstadt). A symptomless but definite hypoglycemia exists in nephrotic children (Knauer). It seems probable, then, that hypercholesteremia is the result of a disturbance of fat metabolism accompanying the nephrotic syndrome and not the cause or the result of edema. A further study of the relation of cholesterol to blood proteins is in progress.

AUTHORS' SUMMARY.

PLASMA PROTEIN, RED-CELL SEDIMENTATION AND SERUM LABILITY OF THE BLOOD IN TUBERCULOSIS. L. R. JONES, Am. Rev. Tuberc. **23**:325, 1931.

In twenty patients with pulmonary tuberculosis, as compared with twenty normal subjects, the plasma protein was found within normal limits. Fibrin was increased in nineteen, and in seven of these globulin was increased. Albumin was within normal limits in thirteen and decreased in seven. In the tuberculous group the average value of the protein quotient was 1.47, and in the normal group, 2.39. Of the tuberculous group, eleven exhibited a protein quotient within normal limits. A quantitative shift of the plasma proteins in the tuberculous patients did not bear any relationship to the type and extent of the involvement. A marked increase in sedimentation of the blood was noted in nineteen of the tuberculous patients, but the amount of the increase bore no relation to the extent or to the advancement of the disease. Increased precipitability of serum protein could not be correlated with the clinical diagnosis. Serum precipitability, though markedly increased in all of the cases of tuberculosis, was not correlated with the ratio of albumin to globulin in the plasma.

H. J. CORPER.

THE VALUE OF DETERMINATIONS OF THE IRON CONTENT OF WHOLE BLOOD. W. P. MURPHY, R. LYNCH and I. M. HOWARD, Arch. Int. Med. **47**:883, 1931.

Determinations of the iron content of the whole blood were made on the blood of a group of persons having essentially normal hemoglobin levels and red blood cell counts, and the figures are herein recorded. The average iron content of the blood in normal young men is 44.84 mg. per hundred cubic centimeters of blood, in normal young women, 42.48 mg., and in a group of sixty persons of both sexes and of varying age with essentially normal blood, 42.74 mg. It is suggested that a figure to be known as the "iron index" be calculated by dividing the figure for whole blood iron by the red blood cell count in millions of cells per cubic millimeter. This figure normally varies between 8 and 9, the average in this series being 8.46. In pernicious anemia, during relapse, the iron index was always found to be above 10, with a tendency to approach normal during a satisfactory remission following treatment with liver. Except in certain unusual circumstances, the iron index was found to be normal or lower than normal in chronic secondary anemia. Only in patients with anemia resulting from acute loss of blood and in certain of the patients with leukemia was the iron index above normal and in the range generally found in pernicious anemia. It is suggested from the preceding observations that the iron index is of definite value in distinguishing between per-

nicious anemia and secondary anemia in most instances, and that the constancy of the figure for whole blood iron in persons with normal blood suggests this as a satisfactory means of following the changes that may occur in the blood during treatment for anemia.

AUTHORS' SUMMARY.

THE LACTIC ACID IN THE BLOOD OF THE NEWBORN. N. J. EASTMAN and C. M. MCLANE, Bull. Johns Hopkins Hosp. **48**:261, 1931.

The lactic acid content of the blood of the fetus in utero is within normal limits. The lactic acid content of the blood of the infant at birth is regularly elevated, the amounts in the present series ranging from 28 to 45 mg. per hundred cubic centimeters, with an average of 35 mg. In the normal infant this increased lactic acid content of the blood at birth is due to simple diffusion from the mother, the lactic acid of whose blood at the moment of delivery is increased as the result of the muscular activity incident to labor. In the asphyxiated infant a very definite endogenous production of lactic acid occurs, the lactic acid of the blood rising above that in the maternal blood to reach a concentration as high as 90 mg. per hundred cubic centimeters. The high concentration of lactic acid of the blood exhibited by asphyxiated infants makes it seem probable that asphyxia neonatorum is associated with considerable acidosis; but in the present state of knowledge one hesitates to draw conclusions as to how important a factor it may be.

AUTHORS' SUMMARY.

LEAD IN FECES AND URINE. F. FRETWURST and A. HERTZ, Arch. f. Hyg. **104**:315, 1930.

The average normal excretion of lead is 0.5 mg. per kilogram of feces and 0.03 mg. per liter of urine. The amounts excreted by lead workers with no symptoms of poisoning may be only slightly higher. Persons with definite symptoms of lead poisoning may excrete as much as 2 mg. per kilogram of feces and 0.07 mg. per liter of urine.

ARTHUR LOCKE.

THE CATALASE ACTION AND GLUTATHIONE CONTENT OF ERYTHROCYTES IN ANEMIAS. EMERICH BACH and ERNST BACH, Biochem. Ztschr. **236**:174, 1931.

The cold reduction of blood is mainly due to glutathione. In true pernicious anemia, the relative catalase and glutathione contents of the erythrocyte are increased. In secondary anemias with preceding cachexia, the catalase and glutathione contents of the erythrocyte are not increased. In acute losses of blood, the relative glutathione content is increased, while the relative catalase content does not change. The value catalase-erythrocytes is independent of macrocytosis and hyperchromatism. The same conditions that cause an increased respiration of the erythrocyte produce also an increase in its catalase and glutathione content. This is interpreted as evidence that catalase is involved in cellular respiration.

WILHELM C. HUEPER.

PHOSPHATIDES AND AMINES OF THE BLOOD IN DISEASES OF THE KIDNEY AND THEIR RELATIONS TO HYPERTENSION. K. HOESCH, Klin. Wchnschr. **10**: 881, 1931.

With the marked hypertension in malignant sclerosis, fixed hypertonicity and chronic nephritis, the amino-nitrogen is increased. The amino-nitrogen is contained to some extent in an ether-soluble uramino acid and base, which are not related to the phosphatides, and which occur in a free state. The increase in cephalin in malignant sclerosis may be due to decomposition processes (lecithin → cephalin). There is no disturbance in the phosphatide content.

AUTHOR'S SUMMARY.

A Method for the Determination of Fibrin, Globulin and Albumin in Blood Plasma. Hugo Theorell and Gösta Widström, Ztschr. f. d. ges. exper. Med. **75**:692, 1931.

The method described permits reliable determinations to be made on as little as 1 cc. of plasma. The method employs nitrogen determinations with hypobromite, after recalcification from citrated plasma in the case of fibrin, and after salting out with magnesium sulphate in the case of globulin and albumin.

Pearl Zeek.

Microbiology and Parasitology

Pernicious Malaria. Ettore Marchiafava, Am. J. Hyg. **13**:1, 1931.

Evidence is presented for the existence of three different types of malaria and for their endoglobular position in the red blood corpuscle. Pernicious malaria occurs solely as a result of infection with Plasmodium falciparum, never in winter or early spring and only as recent infections or early relapses. The proliferation of endothelial cells in the blood stream has its diagnostic importance, as well as being a measure of bodily defense. True tertian fever occurs in these cases, unless the picture is altered by a mixed or multiple infection or by atypicality in the time of the occurrence of sporulation. The sporulation in this type of malaria occurs in the visceral circulation, and the gametocytes appear in the peripheral circulation usually several days after the onset of the fever. The greater pathogenicity of P. falciparum is explained by its shorter period of incubation, more frequent multiplication, greater number of spores, greater toxicity and its resistance to quinine. The clinical and pathologic features of pernicious malaria are presented, as well as the rational therapeutic measures.

P. H. Guinand.

Bacilli of the Genus Hemophilus with Regard to the X and V Growth Factors. Lucile R. Anderson, Am. J. Hyg. **13**:164, 1931.

Bacillus influenzae, hemolytic and nonhemolytic, requires both the X factor and the V factor under aerobic conditions. The four types of hemophilic bacilli studied do not require the X factor for growth under anaerobic conditions, but require the V factor. From their cultural reactions it would appear that the bacilli of influenza carry on a normal existence in mediums containing only the V factor under anaerobic conditions. Not one of thirteen anaerobes tested reacted positively to the benzidine test for peroxidase; of forty-four aerobes tested, all but four, two of which were streptococci, gave a positive reaction. Bacillus influenzae, hemolytic and nonhemolytic, and Hemophilus canis do not produce peroxidase. Bacillus para-influenzae produces peroxidase under both aerobic and anerobic conditions. Banana reacts positively to the benzidine test for peroxidase. All evidence appears to substantiate Fildes' view that the X factor is associated and identical with peroxidase. Evidence is submitted supporting the idea of Davis that there is interaction of the X and V factors.

Note: The X and V factors are both present in hemoglobin. The X factor is heat stable and is closely associated with the iron-containing pigment. The V factor is heat labile, and its nature is not well understood.

Author's Summary.

The Cultivation of Balantidium Coli. Eugene Schumaker, Am. J. Hyg. **13**:281, 1931.

Balantidium coli is facultatively anaerobic. It multiplied as rapidly under strictly anaerobic conditions as under aerobic conditions, but a condition of strict anaerobiasis was not more favorable to growth than an aerobic condition. The growth of Balantidium is not inhibited by an oxygen pressure of 18 pounds (8.2 Kg.) per square inch when this pressure is maintained for thirty-two hours. Tropho-

zoites of Balantidium from an experimentally infected rat were not killed by an oxygen pressure of at least 30 pounds (13.6 Kg.) per square inch maintained over a period of seventy-two hours. Inulin may serve, to a slight extent, as a nutrient carbohydrate for Balantidium in cultures. Potato, wheat, corn, buckwheat and rice starches served equally well for the cultivation of Balantidium. Arrowroot starch was also used successfully in cultures. The parasite multiplied at temperatures from 23 to 41 C.; its optimum seemed to be from 37 to 39 C. Multiplication of the organisms was not markedly inhibited at 41 C., but was greatly reduced at and below 34 C. Balantidium was cultivated successfully for thirty-eight days on a modified medium in which only 3 per cent of horse serum was used.

AUTHOR'S SUMMARY.

THE RELATION OF TEMPERATURE AND HUMIDITY TO THE COURSE OF A B. ENTERITIDIS INFECTION IN WHITE MICE. I. J. KLIGLER and L. OLITZKI, Am. J. Hyg. **13**:349, 1931.

White mice from the same stock and of the same age infected with the same number of organisms of the species Bacterium enteritidis and kept at different temperatures and humidities react differently to the infecting microbes: At a low temperature (from 10 to 12 C.) and a high relative humidity (90) the infection is more severe than at higher temperatures (20 and 30 C.) and the same humidity. The mortality is the same, but the incidence of abscesses of the liver is higher. At 30 C., the mice kept at a relative humidity of 90 are more severely affected than those kept at a relative humidity of 35. At a humidity of 35 and a temperature of 30 C., the development of the infection is more rapid, but it is mild or unapparent, clears up rapidly and leads to relatively few deaths in comparison with infection at a relatively high humidity. At 20 C., a higher humidity seems more favorable than a lower one, but the differences are not marked. It appears that the critical factor is not temperature alone nor humidity alone, but the combination of the two — probably constituting the so-called "effective temperature."

AUTHORS' SUMMARY.

LOCATION OF DENGUE VIRUS IN THE BODY OF MOSQUITOES. R. L. HOLT and J. H. KINTNER, Am. J. Trop. Med. **11**:103, 1931.

Dengue in mosquitoes of the genus Aëdes does not involve any particular part of the insect, but is septicemic. It is believed that the so-called period of "maturation of the virus" of from eleven to fourteen days before the mosquito becomes infective to man is merely the time required for the virus to become of such concentration in the insect as to allow the injection of an infective dose into man. It is believed that this, with the fact that the virus may be transferred from infected to normal mosquitoes for at least three serial transfers, in a form undiminished in its ability to infect man, by feeding normal mosquitoes on a suspension of infected mosquitoes ground up in normal blood, mitigates strongly against the theory held by certain investigators that a cyclic phase in the life of the virus is accomplished in Aëdes. It seems that this mosquito is merely a means of transmission from man to man and is not necessary to the continued existence of the virus.

AUTHORS' SUMMARY.

ATTEMPTS TO PRODUCE BRONCHOMONILIASIS IN MONKEYS. HOBART A. REIMANN and TIMOTHY J. KUROTCHKIN, Am. J. Trop. Med. **11**:151, 1931.

Intratracheal, intravenous and direct inoculation of Monilia tropicalis, isolated from a fatal case of bronchomoniliasis, into the lungs of monkeys failed to induce pulmonary infection. Two normal animals were inoculated intratracheally in attempts to induce a primary infection, without success. In the other monkeys efforts were made to reduce the resistance of the lungs by injection of inert foreign bodies, by actual laceration of the pulmonary tissues and by intravenous

injection of chaulmoogra oil, in the hope that Monilia would grow as a secondary invader in the damaged tissues. Several suggestions to explain the failure to produce lesions may be mentioned: 1. Monkeys may be resistant to infection with Monilia, or the strain used may have been avirulent for these animals. 2. The lung may not have been damaged severely enough to permit the organisms to gain a foothold. 3. The monilias may not have reached the damaged tissue. 4. There was no obstruction in the bronchi to prevent the evacuation of the inoculum. 5. The monilias inoculated were from young cultures, i. e., they were in the yeast-like stage of their life cycle. It has been suggested that in the mycelial, or older, stage the organisms are more resistant and invasive. In another communication, the formation of tubercle-like nodules in the traumatized lungs of rabbits following the inoculation of old cultures of Monilia tropicalis is reported.

AUTHORS' SUMMARY.

THE INTRATRACHEAL INOCULATION OF MONKEYS WITH PNEUMOCOCCI. G. W. STUPPY, I. S. FALK and M. A. JACOBSON, J. Prev. Med. **5**:81, 1931.

Intratracheal inoculation of monkeys of the species Macacus rhesus and Cebus capucinus with varying amounts of virulent pneumococci of type I did not result in lobar pneumonia, although in most cases it brought about an increase in temperature and leukocytic reactions, with pneumococcal septicemia. Recovery usually occurred within a week after inoculation. Only two of thirteen monkeys died of the pneumococcal infection. The lungs were found to be normal, except for an increase in the number of polymorphonuclear leukocytes in the interstitial tissue, blood vessels and bronchi. Intratracheal inoculation of the monkeys with cultures of low virulence, followed by cultures of progressively increasing virulence, gave rise to a slight increase in temperature and in the number of leukocytes, but no septicemia. The absence of septicemia indicated that some immunity had been produced by the previous inoculations of pneumococci of lower virulence. On the whole, Macacus rhesus and Cebus capucinus appeared to be highly resistant to pneumococcal infection.

AUTHORS' SUMMARY.

INTRABRONCHIAL INSUFFLATION OF PNEUMOCOCCI IN RABBITS. G. W. STUPPY and I. S. FALK, J. Prev. Med. **5**:89, 1931.

In rabbits intrabronchial insufflation of pneumococci of uniformly high virulence gave rise to a bronchopneumonia that usually caused death in from two to five days, with septicemia and a generalized distribution of pneumococci in the lungs. In some animals there was acute inflammation of the interstitial tissue of the lung and perivascular and peribronchial lymphangitis. Suppurative bronchitis and pleuritis were only occasionally seen. The factor of resistance to pneumococcal infection among individual rabbits is of importance in determining the type of lesions produced by the introduction of pneumococci into the lung. Attempts to lower resistance by chilling were not successful, as the chilling did not appreciably increase the rabbits' susceptibility to pneumococci, but did apparently predispose them to spontaneous infections, which in the control rabbits (chilled, but not inoculated) were frequently fatal. The lesions induced in the lungs of the rabbits by insufflation of pneumococci of types I, II and III, and of the same degree of virulence (as measured in white mice), were on the whole similar. The virulence of the pneumococcus employed, rather than its serologic type, would appear to be the important factor in the production of infection.

AUTHORS' SUMMARY.

EXPERIMENTAL POLIOMYELITIS. P. H. HARMON, H. J. SHAUGHNESSY and F. B. GORDON, J. Prev. Med. **5**:115 and 139, 1931.

Prior to the onset of experimental poliomyelitis in rhesus monkeys following intracerebral inoculation of virus, changes occur in the body temperature, in the numbers of polymorphonuclear neutrophilic leukocytes in the blood and in the

cell and globulin contents of the cerebrospinal fluid. These changes are analogous to those that occur in poliomyelitis in man. The first constant alteration detectable in the preparalytic stage of the experimental disease is the change in the body temperature. In many, but not all, monkeys the preparalytic increase in the numbers of neutrophilic leukocytes is coincident with the rise in the body temperature; in a few cases the change in the leukocyte count occurs a day or two after the rise in the temperature. Changes in the spinal fluid occur definitely one or two days after the changes in the temperature, except in a few animals in which the two changes are observed simultaneously. Alterations in the velocity of the sedimentation of the erythrocytes occurred only after the onset of paralysis, usually after the monkey was prostrate from an extension of the disease.

Our criterion for abortive poliomyelitis in monkeys is absence of paralysis, but presence of symptoms and of changes in the spinal fluid or of symptoms and of an increase in the body temperature and in the numbers of neutrophilic leukocytes, the symptoms, the changes in the spinal fluid and the increase in the temperature and in the numbers of leukocytes occurring after a period of incubation and resembling those observed in the preparalytic stage of the ordinary form of the disease. Following 555 intracerebral inoculations in 350 monkeys, only 10 cases of abortive poliomyelitis occurred. We found 7 instances of "missed infection," in which a certain dilution of a virus caused no paralysis in a monkey, although a monkey receiving a higher dilution became paralyzed. Some of these may have been cases of abortive poliomyelitis, although they did not conform to our criterion. Two cases in which paralysis occurred thirty-three and fifty-one days, respectively, after inoculation were probably cases of relapsing poliomyelitis. Abortive and relapsing poliomyelitis and "missed infections" seem to be the result of differences in susceptibility in individual monkeys, rather than of mild infection with an attenuated virus.

AUTHORS' SUMMARIES.

EFFECTS ON GUINEA-PIGS OF FILTRATES OF TUBERCULOUS SPUTUM. A. LARSON, J. Prev. Med. **5**:161, 1931.

Filtrates of sputum from tuberculous patients, containing numerous tubercle bacilli, were inoculated subcutaneously into forty-three guinea-pigs, ten receiving a Seitz filtrate, twenty-two a Berkefeld filtrate and eleven a filtrate passed through both Seitz and Berkefeld filters. None of these animals showed the cachexia which is said to be characteristic of the more usual form of infection from filtrates. Neither was there any enlargement of the inguinal lymph glands at the point of inoculation. At autopsy no lesions suggestive of tuberculosis were found. Smears made from the tracheobronchial and retroperitoneal lumbar lymph glands showed no acidfast rods or granules. Control guinea-pigs inoculated with small doses of unfiltered sputum from each patient died with generalized tuberculosis. In these results there is no evidence that tuberculous infection is caused by Seitz or Berkefeld filtrates of sputum. When considered in connection with the numerous negative results of others, these results make it probable that the positive signs of infection that have been reported were due to some other factor than a filtrable virus. The silver plating of the cup of the Seitz filter exerts no appreciable oligodynamic action on suspensions of tubercle bacilli allowed to remain within it for eighteen hours.

AUTHOR'S SUMMARY.

LETHARGIC ENCEPHALITIS: THE GLASGOW EPIDEMIC OF 1923. ASHIE MAIN, J. Hyg. **31**:162, 1931.

The main features of the Glasgow epidemic of encephalitis of 1923 are portrayed in this review. The review is in no sense an intimate neurologic study. The author was sought, rather, to furnish a general impression of the clinical phenomena as they first presented themselves, and to follow the picture as it unfolded itself in the succeeding phases one year and five years later. In this way there have been thrown into relief the characteristics that distinguish epidemic encephalitis

from poliomyelitis and the encephalitis of influenza. A critical summary of the sequelae reveals and illustrates the hypothesis that they are to be explained, not on the assumption of a progressive lesion of the nervous system, such as dementia paralytica, but on the assumption of an initial and permanent damage to the complicated neural mechanism of the midbrain, hypothalamus and basal nuclei. The consequent instability of the mechanism renders it prone to give expression to various forms of disability, depending on ill-defined proclivities, one of which is associated with the age of the patient at the time of the initial attack. However inscrutable its origin and however incalculable its course or obscure the conglomeration of its individual manifestations, there is no difficulty in recognizing the scar it leaves on the health of the community.

FROM THE AUTHOR'S SUMMARY.

Immunology

THE NEUTRALIZATION OR DESTRUCTION OF DIPHTHERIA TOXIN BY TISSUE. A. WADSWORTH and E. N. HOPPE, J. Exper. Med. **53**:821, 1931.

As determined by the intracutaneous test in guinea-pigs, diphtheria toxin is not altered in the presence of cardiac tissue obtained from the fetal or from the adult heart of the guinea-pig. Tissue cultures were apparently uninjured by the presence of the toxin in the dilutions used in these experiments, and, when washed with embryo extract after removal of the diluted toxin, continued to grow. Embryonic guinea-pig cardiac muscle tissue growing in cultures in vitro possesses the power of neutralizing, binding or destroying diphtheria toxin so that it is no longer toxic for normal guinea-pigs. Such neutralization takes place through the intervention of growing tissue and is a property that is lacking in similar surviving tissue not in a state of cultivation. Thus, it appears that the living, growing cells of the tissues neutralize or destroy limited quantities of toxins; only when the quantity of toxin exceeds a certain limit is its action injurious.

AUTHORS' SUMMARY.

ACTIVE IMMUNIZATION AGAINST POLIOMYELITIS IN MONKEYS. M. BRODIE and A. GOLDBLOOM, J. Exper. Med. **53**:885, 1931.

A combination of poliomyelitis virus and specific human serum is effective for the production of active immunity. For each gram of active virus given intradermally as an emulsion, 6 cc. of human immune serum, injected subcutaneously, was required in our experiments to protect a monkey from paralysis. Some degree of active immunity was induced. Immunity, without symptoms of the disease, was secured when the serum was given at the time of inoculation, or within three days preceding or following inoculation of the virus. For the production of immunity, virus, preceded by serum administration, is probably less effective than when it is given simultaneously with, or before, the injection of serum. The virus neutralization test is more sensitive than the direct intracerebral test for determining the production of immunity.

AUTHORS' SUMMARY.

LOCAL SKIN REACTIVITY TO BACTERIAL FILTRATES: PASSIVE IMMUNITY. G. SHWARTZMAN, J. Exper. Med. **54**:1, 1931.

It has proved possible to elicit passive immunity to B. typhosus reacting factors by means of normal and immune homologous neutralizing antibodies. The in vivo serum protection against these factors followed the law of multiple proportions. There was observed a considerable loss of antibodies from the blood stream. Passive immunity was best obtained when the immune serum was injected intravenously half an hour before the intravenous injection of the reacting factors. It was possible to prevent the occurrence of the local skin reaction by an intravenous injection of serum after the intravenous injection of the reacting factors, provided

that the serum dose was very large and that the serum injection was made immediately after the filtrate injection. A number of experiments clearly demonstrated the interesting fact that the greater the amount of antiserum injected intravenously, the more efficient was the in vivo neutralization, in a ratio distinctly greater than the quantitative increase of serum. It is suggested that there may be a practical value of the observation in relation to serum therapy.

AUTHOR'S SUMMARY.

INTRACUTANEOUS PNEUMOCOCCUS INJECTION. J. FREUND, J. Exper. Med. **54**:171, 1931.

Young and adult rabbits react differently to intracutaneous injection of virulent pneumococci. In adult rabbits a very extensive inflammation develops at the site of infection, and bacteremia and death occur only in a relatively few rabbits. Young rabbits fail to develop extensive inflammation and die with bacteremia. It is probable that the fate of the animals is influenced by the capacity to develop inflammation at the site of injection of pneumococci.

AUTHOR'S SUMMARY.

LOCAL ORGAN HYPERSENSITIVENESS (RABBIT'S EYE). D. and B. C. SEEGAL, J. Exper. Med. **54**:249 and 265, 1931.

Rabbit eyes sensitized with guinea-pig red blood cells or fresh egg white respond with an inflammatory reaction following the intravenous injection of the homologous, but not the heterologous, antigen. A multiple antigen containing minute amounts of separate antigens is sufficient to cause this sensitiveness. The reaction has been obtained as long as eight months after sensitization. Repeated daily injections of a single antigen produces no reaction after the first few days, while the injection of various antigens on succeeding days produces inflammation. Permanent desensitization does not occur after eight months unless large doses of antigen are used. The reaction is not due to an initial tissue injury. In the actively sensitized rabbit eye a sterile inflammation may develop after the introduction of the homologous antigen into the gastro-intestinal tract.

EDNA DELVES.

COPPER AND IRON IN IMMUNITY. A. LOCKE and E. R. MAIN, J. Infect. Dis. **48**: 419, 1931.

Neurotoxins appear to be dispersions of bacterial protoplasm containing fragments of a positively charged respiratory substance having copper as the predominant catalyst. They resemble respiratory enzymes of the oxydase type and the proteases of the p_H 8 erepsin type in being inactivated by sodium cyanide and cysteine. The hemotoxins appear to contain fragments of negatively charged respiratory substance having the ferrous iron as the predominant catalyst. They resemble the respiratory enzymes of the dehydrogenase type and the proteases of the p_H 4 papain type, which are not inactivated by sodium cyanide or cysteine, but are inactivated by the cupric ion.

AUTHORS' SUMMARY.

LOCAL SKIN REACTIVITY (SHWARTZMAN'S REACTION) TO PNEUMOCOCCUS "FILTRATES." E. J. COPE and K. M. HOWELL, J. Infect. Dis. **48**:570, 1931.

Filtrates of pneumococci which were not disintegrated gave no Shwartzman skin reactions, while solutions of pneumococci dissolved in bile produced such reactions. No skin reactions were obtained with egg white, dilute bile, ascites broth, spinal fluid and horse serum. Human serum and a mixture of bile, ascites broth and salt rarely produced a reaction. Group specificity of pneumococci was demonstrated in all but one case. The phenomenon of local skin reactivity appears more valuable than agglutination in determining pneumococcal types. Whether each type and strain of pneumococcus has a specific toxic substance, has to be determined.

EDNA DELVES.

SIMULTANEOUS MULTIPLE IMMUNIZATION. L. HEKTOEN and A. K. BOOR, J. Infect. Dis. **48**:588, 1931.

The rabbit is capable of producing many specific precipitins in response to the simultaneous introduction of many single antigens.

AUTHORS' SUMMARY.

SPECIFICNESS OF HEMOGLOBIN PRECIPITINS. L. HEKTOEN and A. K. BOOR, J. Infect. Dis. **49**:29, 1931.

At times antihemoglobin precipitin serum, obtained in response to a pure, single antigen, may react with other hemoglobins than the one that served as the antigen. Such extraspecific action may be overcome by diluting the serum. It appears that hemoglobin may cause responses of wider relationship than those of species.

AUTHORS' SUMMARY.

EXPERIMENTS BEARING ON ACUTE RHEUMATIC FEVER. B. J. CLAWSON, J. Infect. Dis. **49**:90, 1931.

Rabbits made hypersensitive to streptococci can be desensitized by intravenous administration of a streptococcic vaccine. Injections with doses of streptococci that produce marked lesions in hypersensitive animals have little or no effect on vaccinated hypersensitive animals. This protective phenomenon is not strictly type specific, but seems probably species specific. It does not seem to be in the category of a reaction to nonspecific protein. Protection is uniformly associated with a high titer of agglutination, while hypersensitiveness is not. The use of intravenous vaccine treatment in acute rheumatic fever is suggested.

AUTHOR'S SUMMARY.

QUANTITATIVE ASPECTS OF IMMUNITY REACTIONS. J. MARRACK and F. C. SMITH, Brit. J. Exper. Path. **12**:30 and 182, 1931.

The compound of horse-serum pseudoglobulin and its antibody is slightly soluble in 0.9 per cent NaCl solution. The amount of precipitate obtained from mixtures of antigen and antibody in optimum proportions is not affected by moderate variations in the concentration of electrolytes. When antigen is in excess and the volume large, the amount is greatly increased by the addition of 0.1 N$BaCl_2$. This we consider to be due to the neutralization of the negative charge of an insoluble suspension. The amount of precipitate is unaffected by the addition of nonspecific proteins. The precipitate is composed of protein; no substances soluble in fat solvents were detected.

The ratio of antigen to total protein in the precipitate formed in a precipitin reaction increases when increasing amounts of antigen are added to a given amount of antibody. The union of the antigen-antibody compound with more antigen or antibody, when either is added in excess, is not due to nonspecific adsorption. The total amount of precipitate from a given amount of serum and the ratio of antigen to total protein are higher with strong serums than with weak serums. The amount of precipitate and rate of flocculation may be increased by the addition of nonspecific proteins, but the ratio of antigen to total protein in the precipitate is little altered. It is inferred that nonspecific proteins may increase the rapidity and completeness of flocculation of the antigen-antibody compound, but are very little adsorbed.

AUTHORS' SUMMARIES.

IMMUNOLOGICAL DIFFERENCES BETWEEN STRAINS OF POLIOMYELITIC VIRUS. F. M. BURNET and JEAN MACNAMARA, Brit. J. Exper. Path. **12**:57, 1931.

A poliomyelitic virus derived from a child dying in Melbourne has shown distinct immunologic differences from the Rockefeller Institute "mixed virus" strain both in cross-immunity experiments and by neutralization tests in vitro. Three instances are described of monkeys that contracted a typical fatal infection after

injection of the heterologous virus, despite the fact that some weeks previously they had suffered a typical attack of experimental poliomyelitis.

AUTHORS' SUMMARY.

A SPECIFIC PRECIPITATING POLYSACCHARIDE FROM B. DYSENTERIAE (SHIGA). W. T. J. MORGAN, Brit. J. Exper. Path. **12**:62, 1931.

A method is described for the isolation of a polysaccharide from the smooth variant of B. dysenteriae (Shiga). The substance obtained by this method gives specific precipitation with the homologous immune serum up to a dilution of 1 in 6,000,000. The intravenous inoculation of this polysaccharide into a rabbit did not give rise to the production of demonstrable antibodies.

AUTHOR'S SUMMARY.

AGGLUTININS OF TICK-BITE FEVER AND SPORADIC TYPHUS IN SOUTHERN AFRICA. ADRIANUS PIJPER and HELEN DAU, Brit. J. Exper. Path. **12**:123, 1931.

The typhus-like disease in Southern Africa, which we propose to call tick-bite fever, produces agglutinins for B. proteus, OX 19, OX 2 and X Kingsbury. Typhus in South Africa produces agglutinins for OX 19 and OX 2, but not for X Kingsbury. Guinea-pigs infected with either tick-bite fever or typhus develop agglutinins for X Kingsbury, but not for OX 19 nor for OX 2. All these agglutinins appear to become more active if one lets the serums stand for some days. This phenomenon of "temporary inhibition" may explain certain discrepancies observed in agglutination reactions with X-strains. In tick-bite fever agglutinins appear late in the disease.

AUTHORS' SUMMARY.

OBSERVATIONS ON SALMONELLA AGGLUTINATION AND RELATED PHENOMENA. P. B. WHITE, J. Path. & Bact. **34**:325, 1931.

Saline extracts of heated Salmonella bacilli and the carbohydrate haptenes set free from these organisms by antiformin have the same powers of fixing somatic agglutinins as have the bacillary bodies from which they are derived. On the other hand, carbohydrate haptenes prepared by the author's acetic acid method lack appreciable ability to bind the agglutinins of much diluted antiserum.

AUTHOR'S SUMMARY.

AUTOHAEMAGGLUTINATION. W. BOXWELL and J. W. BIGGER, J. Path. & Bact. **34**:407, 1931.

A case of autohemagglutination which occurred in a woman, aged 65, who suffered from anemia and an atypical leukemia, is described. Her serum agglutinated her own cells and the cells of the four blood groups rapidly and markedly at air temperature but not at body temperature. The literature is reviewed, and it is concluded that up to the present only 22 authentic cases of the condition have been described. A new definition of autohemagglutination is suggested as follows: Autohemagglutination is a clumping of erythrocytes into irregular masses, visible to the naked eye, occurring in the presence of the individual's own serum, without bacterial action, at air temperature and reversible at body temperature.

AUTHORS' SUMMARY.

SEROLOGICAL CLASSIFICATION OF MONILIAS. K. STONE and L. P. GARROD, J. Path. & Bact. **34**:429, 1931.

The complement-fixation and precipitin reactions have been applied to the study of monilias. All monilias cultivated from cases of thrush were found identical

when examined by these methods. Of 14 strains of Monilia found in various types of pathologic material and examined by both these methods, 12 were found to be identical with the Monilia of thrush. The application of the same tests to 10 named types of Monilia (Castellani) indicates that 6 of these are identical with the Monilia of thrush.

AUTHORS' SUMMARY.

ACTION OF CONGO RED ON STREPTOCOCCAL AND B. WELCHII HEMOLYSIN. J. GORDON, J. Path. & Bact. **34**:439, 1931.

Certain concentrations of solutions of congo red neutralize the hemolysins of Streptococcus hemolyticus and B. welchii. These neutralizations are reversible; in the case of the streptococcus the addition of cuprammonium artificial silk adsorbs the congo red and liberates the hemolysin. This method cannot be used with B. welchii, as the hemolysin is destroyed by artificial silk. Reversibility with both the hemolysins of S. hemolyticus and B. welchii can be shown by the adsorption of congo red on ox serum. Reversibility is best effected where the concentration of congo red is just sufficient to neutralize the hemolysin. Congo red does not neutralize the hemolytic activities of solutions of saponin, sodium taurocholate or sodium ricinoleate.

AUTHOR'S SUMMARY.

STAPHYLOCOCCUS TOXIN ANATOXIN AND ANTITOXIN. F. M. BURNET, J. Path. & Bact. **34**:471, 1931.

Staphylococcus toxin is rapidly detoxicated by formaldehyde at 37 C. The atoxic preparation (anatoxin) is an effective immunizing agent and is capable of binding antitoxin in vitro. The binding power of a freshly detoxicated preparation is, within the limits of experimental error, accurately half that of the toxin of origin. By the use of anatoxin it can be shown that the toxin-antitoxin and anatoxin-antitoxin reactions are almost completely irreversible within a minute or two of mixing. From the partition of antitoxin between toxin and anatoxin it is deduced that both reactions are of the same molecular order. The toxin-antitoxin neutralization curve for staphylotoxin is described. A discussion of the toxin-antitoxin reaction in general leads to the conclusion that the reaction is primarily a true stoicheiometric union modified by adsorption of the constituent on to aggregates of toxin-antitoxin molecules.

AUTHOR'S SUMMARY.

NEW SEROLOGICAL TYPE OF SALMONELLA. P. H. LESLIE and A. G. SHERA, J. Path. & Bact. **34**:533, 1931.

A new type of Salmonella organism has been isolated by blood culture from a human case of clinical paratyphoid fever. Its antigenic structure, so far as the analysis has been carried, may be expressed in symbols (Bruce White 1926 and 1929) as follows: Specific phase = D_1, D_2 + a minor factor; group phase = G, E_1 and E_2 + minor factors; "O" antigen = III. It is proposed to call this type Salmonella eastbourne.

AUTHORS' SUMMARY.

FRACTIONS OF DIFFERENT ANTITOXIC QUALITY FROM THE SAME SERUM. M. BARR and A. T. GLENNY, J. Path. & Bact. **34**:539, 1931.

A diphtheria antitoxic plasma giving an in vivo value of 950 units and in vitro value of 625 units (ratio, 1:52) has yielded, by successive precipitations with ammonium sulphate, a series of globulin fractions of different antitoxic quality. The ratio of the fractions precipitated by the least amounts of ammonium sulphate is greater than that of the original plasma. The ratio decreases progressively throughout the series from 2.69 in the first fraction to 0.93 in the last.

AUTHORS' SUMMARY.

STUDIES OF PROTECTION AGAINST TUBERCULOSIS. A. STANLEY GRIFFITH, Medical Research Council, Special Report Series no. 152, 1931.

The strain of B C G used in these experiments can produce local lesions in the rhesus monkey, but these are always benign and do not lead to generalization. B C G given by the mouth can pass through the mucous membrane of the alimentary canal into the adjacent glands and also gain access to the blood-stream. Vaccination with B C G, whether by feeding or by injection, has failed to give to monkeys the complete protection against tuberculosis reported by Wilbert, but in some instances may have produced a low grade of relative immunity.

AUTHOR'S CONCLUSIONS.

THE VARIOLA-VACCINIA FLOCCULATION. J. CRAIGIE and W. J. TULLOCH, Medical Research Council Special Report Series, no. 156, 1931.

The variola-vaccinia flocculation reaction is specific and has diagnostic value. The test is made best with antiserum of constant concentration and extract of varied concentration. Treatment of the crusts with ether before extraction with salt solution is of advantage. The reaction is not due to agglutination of secondarily infecting bacteria.

FROM AUTHORS' CONCLUSIONS.

EXPERIMENTAL STUDIES ON FORMATION OF AGGLUTININS AND PRECIPITINS. T. H. AMAKO, Ztschr. f. Immunitätsforsch. u. exper. Therap. **70**:400, 1931.

Rabbits having a high normal antibody titer against certain bacteria responded with a stronger antibody production when immunized with those bacteria than with others. In rabbits revaccinated after an interval, isovaccines had a better immunizing effect than heterovaccines; the antibody response was proportionate to the genetic relationship of the organisms of the revaccination to the bacteria of the original immunization. The withdrawal of blood had a stimulating effect on the titers of agglutinins and precipitins. The development of both antibodies was parallel, but agglutinins appeared somewhat earlier and were more heat-resistant. The absorption of one of the antibodies did not affect the titer of the other.

I. DAVIDSOHN.

VARIABILITY, NOT TYPE SPECIFICITY, IN THE GROUP OF THE PARATYPHOID-FOOD POISONING BACTERIA. HANS MEYER and H. OTSU, Ztschr. f. Immunitätsforsch. u. exper. Therap. **70**:413, 1931.

Following the procedure of Andrewes, it was possible to isolate strains of Bacillus paratyphosus Breslau, which were agglutinated only by a Breslau antiserum and not by other serums, and which were unable to absorb Schottmueller agglutinins. However, immune serum produced with such a specific culture agglutinated also nonspecific Breslau strains and even a few Schottmueller strains. The agglutinins for the different strains could be absorbed separately. The specific strain or "phase" is not an unchangeable characteristic, but a reversible variant of a dominant character with a recessive nonspecific phase, which can reappear any time in the culture or in the antibodies of the immune serum. Therefore, the use of serums produced according to Andrewes' procedure is not reliable for diagnostic purposes.

I. DAVIDSOHN.

A MODIFICATION OF SERODIAGNOSIS OF SYPHILIS WITH INACTIVATED SERUM. TSIEN-YUNG TSÜ, Ztschr. f. Immunitätsforsch. u. exper. Therap. **70**:445, 1931.

Normal rabbit serum is used as source of hemolytic antisheep amboceptor and of complement. Rabbits of equal weight have, in the author's experience, almost equal complement and amboceptor titers, which precludes the necessity of preliminary titration. The patient's serum is inactivated. Comparative tests with other methods showed very good agreement.

I. DAVIDSOHN.

THE SPECIFICITY OF THE SO-CALLED DIAGNOSTIC BACTERIOPHAGES. MARIO E. MASSA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **70**:525, 1931.

A check of the work of Sonnenschein who claimed to have produced specific diagnostic bacteriophages for the Bacterium of Schottmueller, Bacterium dysenteriae and Bacterium typhosum. While some of these bacteriophages preferred certain of the aforementioned bacteria, they invariably acted also on the variants of the other bacteria. The nonspecific lysosensitive variants make the use of bacteriophages for differential diagnosis unreliable.

I. DAVIDSOHN.

INTENSIFYING THE PROPHYLAXIS OF RABIES. OTTO HERRMANN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **70**:536, 1931.

The improvement of mortality records following vaccinations against rabies is due mainly to the broadening of indications for the treatment. The intensifying of the treatment by increasing the dosage and shortening the period to from three to six days is not advisable. Stretching of the same dose over a longer period is preferable.

I. DAVIDSOHN.

IMMUNITY IN TUBERCULOSIS. E. HEDVALL, Ztschr. f. Tuberk. **60**:97, 1931.

Bactericidal antibodies were demonstrated in serum and plasma, but it is believed that they are of little significance in the mechanism of immunity. It was not possible to demonstrate bactericidal action in fixed tissue cells. The mechanism which produces immunity in tuberculosis is probably due to a physicochemic alteration in the cells by which they become less susceptible to tubercle formation when brought in contact with tubercle bacilli. The tubercle bacilli, then, remain virulent in the tissues, but they do not produce disease. Owing to intercurrent diseases or other physiologic disturbances the tissue may lose this resistance against tubercle bacilli, and the previously latent tubercle bacilli may produce progressive disease.

MAX PINNER.

CRITICISM OF B. LANGE'S STUDIES CONCERNING THE CAUSES OF THE LÜBECK DISASTER. R. KRAUS, Ztschr. f. Tuberk. **61**:113, 1931.

It is pointed out that Lange's statement that BCG could not revert to a pathogenic type is unwarranted. Various workers have shown that such reversion does occur, particularly on egg mediums which were used for cultivation in Lübeck. It seems unjustified to conclude that the pathogenic strains that were isolated from dead children were identical with the pathogenic human strain that was kept in Deycke's laboratory at the time of the vaccinations.

MAX PINNER.

Tumors

PURIFIED (PROTEIN-FREE) VIRUS OF CHICKEN TUMOR NO. 1. MARGARET REED LEWIS and WILLIAM MENDELSOHN, Am. J. Hyg. **13**:639, 1931.

Whether the tumor-producing agent is of the nature of a protein cannot be discussed at present. It can be said, however, that no protein detectable by the tests used remained in the solutions of the tumor virus purified by this method. The surmise is that the behavior of the protein-free virus solutions may prove to be different from that of the unpurified tumor extracts. It is hoped that the study of the protein-free virus may lead to a clearer conception of the nature of the virus and, through this, to a better understanding of how the growth of a tumor is brought about.

AUTHORS' SUMMARY.

INTRAVASCULAR HEMANGIO-ENDOTHELIOMA OF THE OVARY. F. W. SOVAK and V. CARABBA, Am. J. Obst. & Gynec. **21**:544, 1931.

Although fifty-two cases of ovarian endothelioma have been reported in the literature, this case is only the fifth of its particular type. A colored woman, 35 years of age, suffered from acute abdominal pain and had a gradually increasing mass in the lower right quadrant of the abdomen. Operation revealed a cystic, lobulated mass, with blood-filled spaces of varying size. Microscopic examination showed a complex tumor, the cellular unit being a small, rounded or flattened, oat-shaped cells. Among the tumor cells were thin-walled blood vessels, evidently derived from the cells. In other areas the cells formed spaces widely dilated with blood.

C. G. WARNER.

TUMORS OF THE CAROTID BODY. F. W. RANKIN and W. L. A. WELLBROCK, Ann. Surg. **93**:801, 1931.

The carotid body is a triangular collection of cells connected by fine fibrous strands, with the oral epithelium on one end and the thymus on the other. Embryologically, it is supposedly developed from the epithelium of the pharynx, from the walls of blood vessels and from nerve tissue or from sympathetic ganglion cells of the carotid plexus. Physiologically, little is known about it. Tumors of this body have been designated by such names as adenoma, endothelioma, perithelioma, paraganglioma and simply tumor of the carotid body. The authors give a comprehensive review of the literature and add twelve new cases of carotid tumor, one bilateral. The characteristic structure of these tumors of the carotid body is that of alveolar perithelioma, with whorls of polyhedral and granular cells, or compact groups with or without lumen, surrounded by endothelioma. The tumor is usually vascular, with the blood spaces lined by prominent endothelial cells. About 80 per cent are benign, rarely metastasizing, occasionally recurring. In one case there were metastases in the liver. Of the twelve cases reported by the authors, five were malignant and six were benign; the bilateral case is interpreted as malignant on one side and benign on the other. The criteria for malignancy are: variation in the size of cells; hyperchromatic nucleoli; mitosis; invasion of the capsule by the tumor. Whether benign or malignant, the tumor is slow in growth.

C. G. WARNER.

SACRAL CHORDOMA. J. A. DICKSON and C. A. LAMB, Ann. Surg. **93**:857, 1931.

Chordoma is a tumor arising from the cellular remains of the notochord and occurring, therefore, along the spine, most frequently at its extremities. The average age of onset is from 35 to 40, the spheno-occipital chordomas appearing, on the average, ten years later than the sacrococcygeal. The tumor is twice as frequent in males as in females. Chordoma has been produced experimentally in rabbits by puncturing the body of a vertebra. Grossly, the tumor appears well encapsulated, rounded or lobulated, with mucoid degeneration in the lobulated cellular areas. Frequently cells of syncytial type are embedded in mucin, some areas resembling colloid carcinoma. Rarely is mitosis present, and only occasionally metastasis. The case reported in this article was treated after operation with deep x-rays, with a progressive decrease in size and a gradual hardening and calcification.

C. G. WARNER.

MENINGEAL FIBROBLASTOMA (DURAL ENDOTHELIOMA, MENINGIOMA, ARACHNOID FIBROBLASTOMA). CHARLES A. ELSBERG, Bull. Neurol. Inst., New York **1**:3, 1931.

Meningeal tumors are supposed to grow from arachnoid cells normally present in the form of clusters or nests in the tissue spaces of the dura mater. The study of tumors of the spinal meninges makes such a postulate, according to Elsberg, not altogether tenable, for such tumors arise also outside the spinal

dura, or on its inner surface, without demonstrable connection with the arachnoid tunic. Elsberg suggests that the origin of the tumors is to be sought in misplaced mesenchymal cell rests. Of the several names suggested, he prefers that of fibroblastoma. The present contribution is based on a study of 100 cases — 50 of cranial and 50 of spinal tumors. They are usually slowly growing, affording the brain an opportunity to adjust itself to the changed conditions. Elsberg differentiates three types: hard tumors, well encapsulated, causing atrophy of the convolutions by pressure; soft tumors, which possess a thin limiting capsule, and which for this reason may invade the sulci and separate the convolutions — the tissue of the soft tumors is fragile and usually very vascular — and tumors combining the features of these two; that is, several well encapsulated tumors connected by soft masses. The intracranial pressure, though increased in the presence of these tumors, is usually not high. It is much less than with the subcortical infiltrating tumors. In experienced hands, if the operation is well planned, the removal of a meningeal tumor is followed by brilliant results.

GEORGE B. HASSIN.

MOUSE LEUKEMIA. E. C. MACDOWELL and MAURICE N. RICHTER, J. Cancer Research **14**:434, 1930.

Susceptibility to inoculated leukemia is a dominant character in mice; in the backcross to a resistant strain there is a segregation of susceptibility and resistance. Two different lines of inoculated leukemia give different proportions of susceptible mice in the backcross. With the inoculated leukemia from line I, the proportion of susceptible mice is consistently lower than is expected for a single gene, and considerably higher than is expected for two or more independent genes. The hypothesis that there are two linked genes is being tested. With the inoculated leukemia from line A the proportion of susceptible mice in the backcross is always less than when line I is used. But changes in line A itself result in different proportions in different periods; this necessitates interpreting the different periods independently, but such interpretations are not amenable to satisfactory genetic verification.

AUTHORS' SUMMARY.

AN HISTOLOGICAL STUDY OF SALIVARY GLAND TUMORS. A. A. THIBAUDEAU and E. M. BURKE, J. Cancer Research **14**:440, 1930.

In salivary tumors the histologic picture in no way aids in the determination of the relative malignancy or of the outcome. The outcome seems to depend on the clinical aspects of the case, with special reference to the extent of the local infiltration and the duration of the tumor.

B. M. FRIED.

TUMORS IN CAPTIVE PRIMATES (GIANT CELL TUMOR IN A CHACMA BABOON). HERBERT L. RATCLIFE, J. Cancer Research **14**:453, 1930.

The case of a malignant tumor in a primate in captivity which is described in this article, is the seventh on record. The growth originated near the lower epiphysis of the ulna, perforated the shaft and the articular cartilage and infiltrated the surrounding tissue. It grew rapidly, metastasizing to the lungs, the heart and the gluteus muscle. The tumor was made up of large spindle cells, numerous capillaries and giant cells. The author did not succeed in transferring the neoplasm to Macacus rhesus.

B. M. FIELD.

PRIMARY MALIGNANT TUMOR OF THE URETER. M. J. RENNER, Surg., Gynec. & Obst. **52**:793, 1931.

The author reports what he considers to be a carcinosarcoma of the ureter. This tumor was found in a man 71 years old. The growth originated from

approximately the middle half of the posterior wall of the right ureter, filling the ureter and penetrating into the bladder. The mass in the bladder measured 7 by 4 by 3.5 cm. Histologically, the growth consisted of carcinomatous islands surrounded by myxosarcomatous and cartilaginous tissue.

C. G. WARNER.

LYMPHOSARCOMA OF THE NECK. JOHN W. SPIES, Surg., Gynec. & Obst. **52**: 815, 1931.

Attention is called to certain types of metastatic carcinoma that may readily be confused with lymphosarcoma of the cervical lymph nodes. In a series of fifty cases diagnosed as lymphosarcoma of the neck, five cases of metastatic carcinoma were found, three of which were classed as lympho-epithelioma; the other two were classed as transitional cell carcinoma. These tumors are radiosensitive. Their primary sites are in the nose, pharynx and mouth.

C. G. WARNER.

ALTERATION OF MALIGNANCY IN METASTATIC GROWTHS AFTER REMOVAL OR IRRADIATION OF PRIMARY GROWTHS. RALPH G. MILLS, ALBERT C. BRODERS and HAROLD D. CAYLOR, Surg., Gynec. & Obst. **52**:824, 1931.

The system of grading carcinomas devised by Broders has been applied to the study of a series of fatal cases, to detect, if possible, the potency of various factors that may affect metastatic growths and even the viability of carcinomatous masses.

Alterations in the histologic structure of malignant metastatic growths might be expected to be found, if longevity after operation or after treatment by irradiation is dependent on changes in the cell.

Evidence was not found that removal of the primary growth or irradiation altered, to an appreciable degree, the histologic structure of metastatic malignant growths.

Irreconcilable variation between the grade of the primary malignant tumor and that of the metastatic growths, between different portions of the same primary growth, or between different metastatic growths of the same subject occurred in 32 of 207 cases (the entire series of cases was 225, in 50 of which the variation persisted after the second survey; 18 of the 50 were finally excluded from the series because the question of multiple primary tumor entered in). The cause of this variation seemed to be inherent in the carcinoma rather than connected with the etiologic factors that surrounded it. Growth of metastatic masses in the lung seemed to be slightly inhibited by ecologic factors in the lung, but there was no noticeable influence exerted by any other organ on metastatic growths that developed within it.

A method of approach has been developed that should be applied to a much larger series of cases, in order properly to analyze the factors involved.

AUTHORS' SUMMARY.

INCIDENCE OF CANCER OF THE BLADDER AND PROSTATE IN CERTAIN OCCUPATIONS. S. A. HENRY, N. M. KENNAWAY and E. L. KENNAWAY, J. Hyg. **31**:125, 1931.

In persons pursuing eight of ten occupations associated with exposure to coal gas, tar, pitch or soot, the incidence of cancer of the bladder is greater than in the general male population, and in persons following five of the ten occupations it is from one and a half to four times as great. Three of these occupations show the highest figures for incidence of cancer of the bladder observed among the forty-six occupations investigated. Various possible sources of error in these figures are discussed, of which the most serious is the smallness of the numbers of deaths involved. The corresponding data for cancer of the prostate give less consistent indications of an occupational liability. The subject needs much further inquiry,

but it has seemed best to publish now, without further delay, such material as is available, rather than wait for another long term of years while more data accumulate.

AUTHORS' SUMMARY.

Medicolegal Pathology

FATAL POISONING WITH ARECALINUM HYDROBROMICUM. HEINSEN, Deutsche Ztschr. f. d. ges. gerichtl. Med. **17**:67, 1931.

Arecalin is an alkaloid of Areca catechu. Poisonings with this drug were unrecorded in the literature to date. Its pharmacodynamic action is similar to that of pilocarpine. In the case described, the autopsy disclosed marked edema of the lungs and large quantities of mucous secretion and foam in the respiratory tubes. There was arterial hyperemia of all the internal organs, with definite signs of internal asphyxiation of the tissues. This case teaches that 50 mg. of arecalinum hydrobromicum causes the death of a healthy adult man within from seven to twelve hours. The poisonous action of this drug is greater and more intense than that of pilocarpine hydrochloride.

E. L. MILOSLAVICH.

DETERMINATION OF ALCOHOL IN BLOOD AND BRAIN. H. KLAUER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **17**:89, 1931.

All the present methods of determining alcohol, quantitatively or qualitatively, are of little value to forensic medicine, because they are either inaccurate or too complicated. To date, the most favored methods used are that of Nicloux, oxidation of alcohol by potassium bichromate in a sulphuric acid solution, and the interfereometric procedure of Kionka and Hirsch; but even these are not satisfactory. A new technical method is introduced by the author and should be consulted in the original paper.

E. L. MILOSLAVICH.

SPATTERING OF TISSUE FROM GUNSHOT WOUNDS. WALDEMAR WEIMANN, Deutsche Ztschr. f. d. ges. gerichtl. Med. **17**:92, 1931.

Not uncommonly, blood, particles of muscle or of fat tissue or small fragments of fractured bone may be hurled out of a gunshot wound and then be found, even after a long period of time, on various objects in the environment of the victim or on the clothing or body of the assailant. Spattering of such tissues is seen particularly on the weapon itself, and then not only on its outer surface, but also within the barrel. Of course, such particles may lodge on the hand that pulled the trigger. Injuries to the fingers or smudging of the same are occasionally observed on the hand that has fired a pistol, as, for example, in a suicide. Spattering of torn tissues of a gunshot wound is seen under certain circumstances, such as in the use of firearms of large caliber, in instances of the abundant development of explosive gases that penetrate the wound canal, and in cases in which the bullet strikes a bone that is close to the skin, thus hindering the expansion of explosive gases. In the last instance, the gunshot wound exhibits a star-shaped appearance. In wounds of this character, one should search for spatters of tissue. In gunshot injuries of larger blood vessels or of the eyeball, spattering of blood or of crushed tissues of the eye may be pronounced, on account of the hydrodynamic action of the fluid medium.

E. L. MILOSLAVICH.

NECROSIS OF LIVER FROM INDIRECT INJURY. J. GERBER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **17**:106, 1931.

Approximately one third of all blunt injuries to the abdomen cause injuries to the liver, particularly to the convexity of the right lobe. The author describes the development of necrotic areas in the subcapsular region on the convexity of

the liver in a young pregnant woman who died of complications (hemothorax) following gunshot wounds of the right side of the thorax. As predisposing factors for the indirect transmission of the force to the liver are mentioned the gravidity hyperemia of the liver, its high position and the limited expansion of the diaphragm, owing to the enlarged gravid uterus. There is a certain analogy to the injuries of the internal organs occasionally found in tangential gunshot wounds of the wall of the thoracic and abdominal cavities.

E. L. MILOSLAVICH.

CHRONIC INDUSTRIAL RADIUM POISONING IN JOACHIMSTHAL. A. WOLDRICH, Med. Klin. **27**:17, 1931.

A special investigation has revealed that many workers in the Joachimsthal mines suffer from a secondary myelotoxic anemia, undoubtedly due to the radium in the minerals.

TRAUMATIC HEMORRHAGE IN THE WALLS OF THE FOURTH VENTRICLE. O. BERNER, Norsk mag. f. lægevidensk. **91**:1155, 1930.

Berner claims that slight trauma may cause hemorrhages in the region around the fourth ventricle, and that even the changes in tension originating during spontaneous bleeding are under certain conditions sufficient to cause analogous hemorrhages. At the time of the trauma, there occurs in the fluids in the lateral ventricles a wave movement, which, seeking to escape, transplants itself through the aqueduct of Sylvius and strikes the floor of the fourth ventricle with such force as to cause lesions there (Duret). The phenomena from the circulatory organs and from the respiratory side so characteristic in the picture of concussion of the brain are thus, he says, easily explained by hemorrhages in the region where the centers of these functions are situated. He discusses where in the brain spontaneous bleedings are known to occur, with particular attention to the so-called "primary ventricular" hemorrhages which originate from the choroid plexus or from a subependymal blood vessel and thus may enter the cranial cavity without destruction of nervous tissue, and treats of the probability of a spontaneous origin of a hemorrhage in the fourth ventricle.

POSTTRAUMATIC TARDY HEMORRHAGES OF THE BRAIN. FRANCIS HARBITZ, Norsk mag. f. lægevidensk. **92**:501, 1931.

Harbitz says that practical experience shows multiple hemorrhages and contusions at the base of the fourth ventricle to be unusual even after marked traumas of the head with pronounced changes in the cranium and surface of the brain; he has sometimes, though seldom, found hemorrhages in the inner portion of the brain simultaneously with contusion of the cortex, meningeal bleeding and fissures in the cranium, as after automobile accidents, but never certain or highly probable traumatic hemorrhages in the walls of the third and fourth ventricles as the only essential result after a moderate trauma of the head, with concussion of the brain as the cause of death (see Berner: *Norsk mag. f. lægevidensk.* **91**:1155, 1930), and he regard such results as rare and hardly of practical significance. In his opinion, Berner stresses too much these small traumatic hemorrhages in the fourth ventricle as the cause of death when there are other evident changes in the brain that can both explain the symptoms and be the cause of death, and in cases with intoxication the possibility cannot be excluded that the changes and death might be due to alcoholism. He agrees with Berner that in concussion of the brain real anatomic changes are doubtless far more frequent than supposed, and more attention to such changes in the walls of the third and fourth ventricles is now advised. With regard to tardy hemorrhages on a traumatic basis, in his material only two cases to date have revealed what might plausibly be considered as late hemorrhages of traumatic origin, and they occurred in work worn men, aged 42 and 55, respectively.

Technical

A New Method for the Determination of Cholesterol. A. Bloch, Schweiz. med. Wchnschr. **61**:108, 1931.

The method originally proposed by Bloor (*J. Biol. Chem.* **24**:227, 1916) for the colorimetric determination of cholesterol in blood, while widely used for many years as a standard procedure, was not universally accepted, because of the time required to make the test, the volume of the reagents required and the frequency with which an undesirable brown contamination would appear during the final stage of the development of color. Apparently unaware of the several existing modifications of the original Bloor method that have appeared within recent years, notably that of Sackett (*J. Biol. Chem.* **64**:203, 1925), which requires only 0.2 cc. of blood, is far simpler and more rapid and yields an excellent preparation for colorimetry, Bloch proposes an additional modification that requires the preliminary separation of the cholesterol on precipitated barium carbonate. One cubic centimeter of the serum is heated on a water bath for one hour with 20 cc. of 10 per cent barium hydroxide. After cooling and filtration, the precipitated material is allowed to dry. The cholesterol is then removed from the precipitate by prolonged extraction with a mixture of alcohol and ether. An aliquot volume of the extract is evaporated to dryness and the chloroform-soluble fraction of the residue converted into the familiar green end-product of the Liebermann-Burchard procedure. Precipitation with the Folin-Wu deproteinization reagent may be substituted for precipitation with barium hydroxide.

Arthur Locke.

Smear Preparations in Lymphatic Leukemia. K. A. Heiberg, Centralbl. f. allg. Path. u. path. Anat. **50**:101, 1930.

From studies on the blood of six normal people and three suffering from chronic lymphatic leukemia the author concludes that the nuclei of only 10 per cent of the small lymphocytes of normal people are greater in diameter than 10 microns, whereas from 37 to 50 per cent of the lymphocytes of those ill with leukemia are larger than 10 microns. He asserts that distortions of as much as 150 per cent occur in the cells of sections. He thinks that smear preparations carefully made yielded the more accurate results.

George Rukstinat.

A Method for Investigating Pathologic Alterations in Bone Structure. L. S. Frank-Kamentzky and W. J. Schlapohersky, Centralbl. f. allg. Path. u. path. Anat. **50**:133, 1930.

The authors employed roentgenograms of thin sections of bone in their studies. Photographs of the changes noted in rickets, osteitis deformans and chronic osteomyelitis and of changes observed post mortem illustrate the potentialities of the method first employed by Julius Wolff in 1900.

George Rukstinat.

Frozen Unfixed Tissue Sections for Histologic Study. O. Schultz-Brauns, Centralbl. f. allg. Path. u. path. Anat. **50**:273, 1931.

Unfixed tissues were cut on the freezing microtome with the added agency of a second freezing apparatus that cooled the knife. From the knife the sections, still frozen, were transferred to slides. In this way friable material, such as placenta, and sticky substances, such as mucus and fat, can be cut and the sections handled with ease. A second advantage of the method is that sections are placed on the slides in the original state without displacement or partial solution of any of the constituents. After being transferred to a slide, the sections can be fixed quickly and individually. The method eliminates fixation of numerous blocks and guarantees complete fixation, which is hard to achieve in the center of a block.

George Rukstinat.

A Modification of Cajal's Gold Sublimate Method for Demonstrating Macroglia Cells in Formaldehyde-Fixed Material. M. Corten, Centralbl. f. allg. Path. u. path. Anat. **50**:339, 1931.

The steps in this staining method are as follows:

1. Cut frozen sections of formaldehyde-fixed material, not thicker than 25 microns.

2. Immerse in the following mixture: ammonium bromate, 15; formalhehyde (neutral), 100, and distilled water, 400. Warm until the mixture steams.

3. Transfer without washing to: antiformin, 3 cc.; distilled water, 2 cc., and alcohol (96 per cent), 8 cc. Keep the sections in motion in this solution for from six to fifteen seconds.

4. Wash twice quickly in distilled water and then place in 1 per cent aqueous gold chloride, 4 cc.; 5 per cent aqueous silver nitrate, 8 cc., and distilled water, 6 cc. Keep in the dark at 37 C. for one hour or until adequately impregnated.

5. Wash in 5 per cent sodium thiosulphate for fifteen minutes, wash in water, dehydrate, clear in xylene and mount in balsam.

The results are similar to those obtained by the original method of Cajal. The modification is applicable to gelatin sections, if the concentrations of gold chloride and sublimate are slightly altered.

George Rukstinat.

Death After Transfusion of Blood. H. Wildegans, Deutsche med. Wchnschr. **56**:2031, 1930.

Severe reactions follow about 5 per cent of transfusions of blood regardless of whether typing is done or not. Errors in typing may occur because the serum is exposed to sunlight or because of alkali in the test tubes. Theoretically a transfusion can be undertaken without accident if the red blood cells of the donor are not agglutinated by the serum of the recipient. Other factors must, however, be considered. In some cases, the blood of the recipient is in such a small volume that it cannot effectively dilute the blood of the donor. For this reason transfusions should never be given in quantities greater than one fifth of the donor's total circulating blood. Wildegans advises administering a saline or a dextrose solution as a preliminary procedure and then calculating, from the difference in the reading of hemoglobin before and after this transfusion, the volume of the blood of the recipient. Agglutination has been observed to occur in titers of 1:250. An important feature in death occurring shortly after a transfusion is the presence of hemoglobin in the kidney, as emboli in the glomeruli and as casts in the tubules. In biologic processes hemolysis can occur in the absence of agglutination, and this suggests a simple hemolysis test to make the tranfusion of blood safer.

George Rukstinat.

Society Transactions

NEW YORK PATHOLOGICAL SOCIETY

Regular Meeting, April 23, 1931

LEILA CHARLTON KNOX, *President, in the Chair*

TWO UNUSUAL CASES OF INTERSTITIAL MYOCARDITIS. MAX LEDERER.

CASE 1.—The patient, a boy, was born at full term but was delivered by forceps, and was formulae-fed. At 7 months of age he began to have diarrhea, which was controlled by diet. At 9 months, he had another attack of diarrhea, with from four to eleven loose, watery stools, showing mucus, but no blood which had lasted for ten days when he was admitted to the hospital. In these ten days he had lost 3 pounds (1.4 Kg.).

He was very poorly nourished, dehydrated and apathetic. The breathing was rapid and shallow, the eyes sunken and the fontanels depressed; there was no cyanosis. The extremities were normal. There was an inconstant, but marked, lateral strabismus of the right eye. The tongue was dry; the tonsils were normal; the cervical and inguinal lymph glands were palpable. The chest was poorly developed; the lungs were normal; the intercostal spaces were prominent. The following observations were made regarding the heart: The point of maximum impulse was in the fifth intercostal space in the nipple line. On percussion there was no enlargement. On auscultation the sounds were rapid and of poor quality; there were no murmurs. The second pulmonic sound was louder than the second aortic.

The urine showed 1.4 per cent sugar, a faint trace of albumin and a trace of acetone. On subsequent examination the urine was clear. The hemoglobin was 82 per cent; the red blood cells numbered 4,500,000; the white blood cells, 18,000, with lymphocytes 81 per cent. The white count varied between 6,100 and 18,000, with from 18 to 57 per cent polymorphonuclears. Nose and throat cultures were negative for diphtheria bacilli. The tuberculin reaction was negative. Stool cultures showed colon bacilli. Repeated roentgenograms of the chest were negative.

Because of the strabismus a spinal puncture was done, and the fluid was found to be normal. The child was placed on an appropriate diet, given two transfusions and within seven weeks was discharged, apparently normal.

The diagnosis on discharge was diarrhea with intoxication and acute catarrhal otitis media.

The child was readmitted nearly one year later. During the interval he had had two mild attacks of tonsillitis, and two months before readmission diarrhea, with twelve stools per day. Two months before admission he had been fretful and had had a temperature of from 101 to 104 F., without chills. Ten days before admission his gums had become swollen and covered with yellow pus. Blisters appeared on the tongue. There was no bleeding. He was fretful and did not eat. The stomatitis was treated, without improvement.

The pertinent findings were swelling and redness of the left eyelid, with a thick, yellow, purulent discharge, and injection of the conjunctivae. The right eye was normal. From the mouth emanated a fetid odor. The tongue was coated and denuded in small areas. The gums were swollen and bled easily. There were no ulcerations. The pharynx was red. The tonsils were large and cryptic. The heart showed no enlargement. The point of maximum impulse was in the fifth intercostal space, just within the nipple line. There were no thrills or murmurs.

The sounds were rapid, irregular and almost tick-tack in quality. There was a suggestive blowing quality to the first apical sound. The second apical sound was accentuated. The pulmonic second sound was accentuated and louder than the second aortic. There were a few discrete, enlarged lymph nodes, in the cervical, axillary and inguinal regions.

The urine showed a faint trace of albumin and acetone. The hemoglobin ranged between 64 and 51 per cent; the red blood cells, between 3,100,000 and 3,450,000; the white cells, between 20,200 and 9,000, with 68 to 59 per cent polymorphonuclears. The bleeding time was one and a half minutes; the coagulation time, three minutes. The tuberculin test was negative up to 5 mg. Cultures from the nose and throat showed the usual organisms; those from the mouth showed a predominance of streptococci. The temperature ranged between 99.4 and 104 F., in a septic fashion. The pulse rate fluctuated between 110 and 132 and the respirations between 28 and 60.

Shortly after admission signs of bronchopneumonia developed, and death followed on the eleventh day.

Autopsy.—The body was that of a well developed, well nourished white boy, 21 months old. The lower extremities were slightly edematous. The abdominal cavity contained between 1 and 2 liters of pale yellow, clear fluid. The peritoneum was pale, smooth and glistening. Both pleural cavities contained small amounts of a similar fluid. The pericardial sac was filled with a similar fluid, causing moderate distention. The thymus and the lungs were edematous, the lungs containing a moderate number of pigment macrophages.

The heart was enlarged, weighing 100 Gm. Externally the right ventricle was distorted by a smooth, round mass that occupied the upper anterior aspect of the right ventricle, close to the interventricular septum. It was nodular and firm. When sectioned, this area was found to consist of a rather well circumscribed, homogeneous, firm, but not hard, yellow tissue embedded in the wall of the myocardium, displacing the epicardium outward and the endocardium inward. The nodule measured 2 by 3 cm., and extended upward to the base of the left cusp of the pulmonary valve, without involving it or impairing its efficiency. There was a similar nodule of the same size embedded in the anterior wall of the right ventricle near the apex. At this point the endocardium and papillary muscles appeared as white structures. The myocardium as a whole was pale. The foramen ovale and the ductus arteriosus were closed. The tricuspid, pulmonary, mitral and aortic valves were normal. The pulmonary artery, aorta and coronary vessels, as well as the auricles, appeared normal.

Numerous sections were taken from various parts of the organ and fixed in alcohol, formaldehyde, Zenker's and Helley's fluids. They were stained with hematoxylin-eosin, van Gieson's stain, Mallory's stain and aniline blue for Aschoff bodies, elastic tissue, tubercle bacilli, Spirochaeta pallida and other bacteria. A study of the sections revealed what appeared to be a progressive inflammatory process passing through successive acute, subacute and chronic stages, with final replacement of the parenchyma by scar tissue. In the acute lesions was seen an interfibrillary infiltration of the musculature with polymorphonuclear neutrophils, accompanied by edema. The muscle fibers in these areas were thinned, as though compressed, and appeared to be undergoing necrosis. The cells were distorted; striations had disappeared, and in places only fragments of cells could be recognized. In the subacute stage, the muscle elements had almost completely disappeared, having been replaced by large collections of numerous plasma and round cells, a few eosinophilic polymorphonuclears and an occasional giant cell. In the chronic stage, the exudate consisted almost exclusively of small round cells and many fibroblasts, the muscle cells having completely disappeared. The stroma was loose, and fibrous tissue strands could be recognized. In the final stage, all that remained was dense fibrous tissue, containing newly formed blood vessels, a few round cells and no muscle. The endocardium, pericardium and blood vessels were normal.

No Aschoff bodies, tubercle bacillus, Spirochaeta pallida or other bacterium could be found.

The mediastinal and mesenteric lymph glands were soft, enlarged and pink. On miscropic examination, the normal architecture was exaggerated. The lymphoid follicles were small, but well developed. The germinal centers showed a variety of changes, ranging from hyperplasia to fibrosis and hyalinization. Some were increased in size owing to proliferation of their component cells; in others, the cells were necrotic. The necrosis varied from that of mild degree to complete destruction of cells and replacement by detritus and nuclear fragments and in some areas fibrosis and hyalinization. The pulp was congested and edematous. The spaces were large and filled with small round cells. In the mesenteric nodes were only moderate numbers of macrophages.

The spleen weighed 50 Gm. It was normal in shape, purple and firm. The capsule was smooth. On section, the follicles stood out prominently. The pulp was dark red and appeared congested.

Microscopically, the architecture of the spleen was normal. In the lymph follicles were changes resembling those in the lymph nodes. In the spleen, however, the changes were more severe, and involved more follicles than in the lymph nodes, The pulp was congested and contained numerous small hemorrhages. The walls of the sinuses were thickened, the thickening being accompanied by marked endothelial hyperplasia.

The capsule of the liver was pale, smooth and glistening. On section, the cut surface presented a widely diffuse, yellow appearance.

Microscopic sections showed the capillaries to be greatly dilated, thereby causing marked distortion of the liver cords. The hepatic cells were swollen in some places and compressed in others. They showed fatty degeneration and infiltration. Areas of focal necrosis, some in early stages, with destruction of the liver cells and invasion with polynuclear cells, others with round cell infiltration and still others with fibrotic changes, were scattered throughout the organ. In the portal areas were an abundant round cell infiltration and a moderate increase in fibrous tissue. The bile passages, except for an apparent increase in the diameter of their lumina, were normal.

The common duct was patent, as were the hepatic ducts. The gallbladder and cystic duct were absent; a thin fibrous band of tissue represented the site where this organ is normally found. The hepatic artery and the portal vein were normal.

The kidneys weighed 60 Gm. each. The capsules stripped with ease, leaving smooth, pale, lobulated surfaces. The cut surfaces of the organs showed the cortex and medulla well differentiated, but pale. The blood vessels were congested. The pelves were normal.

Microscopic sections showed most of the glomeruli to be normal. Scattered throughout the organs, however, were glomeruli that showed changes: some were congested, enlarged and hyperplastic; others showed typical cresent formation and lesions indicating transformation from early cresent formation to complete fibrotic replacement of the tufts. No cellular exudate could be found. The tubular epithelium was swollen and somewhat granular. The blood vessels were normal.

Anatomic Diagnosis.—The anatomic diagnosis was: acute, subacute and chronic interstitial myocarditis; congenital absence of the gallbladder and cystic duct; toxic necrosis of the lymphadenoid tissue (lymph node and spleen); subacute and chronic glomerulonephritis; interstitial hepatitis, and chronic passive congestion and focal necrosis of the liver.

CASE 2.—A boy, aged 13 years, complained of weakness in the legs, chills and fever, vomiting of four days' duration, difficulty in breathing, bloody stools and hematemesis.

The patient was one of nine children; the others were living and well. He had had pneumonia when he was 6 years old. Two weeks before admission to the hospital on Nov. 30, 1930, during a football game he was hit with the football in the right upper quadrant of the abdomen. The next day, he noticed weakness of the legs. That night he was unable to eat and vomited yellowish fluid. He felt

no pain in the upper right quadrant, but noticed that it was black and blue. The next night he complained of pain in the epigastrium and felt feverish. He went to school until November 24, and then remained at home because of his illness.

On the twenty-sixth he began to have chills, which lasted one-half hour and were followed by fever. The weakness in his legs continued. On the twenty-seventh, he noticed that his stools were watery and black, and he coughed up a few firm, red pieces of blood. On the twenty-ninth, he began to have difficulty in breathing, because of pain. There was no cough or expectoration.

Physical examination showed the boy lying in an orthopneic position, apparently acutely ill, with rapid, shallow respirations and dilatation of the alae nasi. He had a cyanotic flush on his cheeks. The cervical lymph glands were palpable and enlarged. Abnormal venous pulsation was noted in the neck. The thyroid gland was not palpable. The chest was well developed. The respirations were rapid and shallow. There was some dulness at the base of the right lung, where the breath sounds were diminished. The heart sounds were rapid, but regular in rate and rhythm. There was an occasional dropped beat. The sounds were of good quality. There were no murmurs. The heart was not enlarged to percussion. The abdomen showed tenderness and rigidity in the upper right quadrant on deep palpation. The edge of the liver was palpable at the umbilicus.

The temperature on admission was 99 F., and during the stay in the hospital ranged between 99 and 101 F. The pulse rate varied between 96 and 138. The respirations were between 26 and 50.

The blood count on admission showed 2,440,000 red blood cells, 16,200 white blood cells, with 72 per cent polymorphonuclear leukocytes, and hemoglobin, 68 per cent. The blood culture was sterile. The Wassermann and Kahn tests were negative. Blood was present in the stools.

During his stay in the hospital, the patient began to show symptoms and signs of cardiac decompensation, and he died on Dec. 8, 1930.

Autopsy.—The body was well developed and well nourished. The peritoneal cavity contained a large quantity of straw-colored, clear fluid. The right pleural cavity was obliterated by dense adhesions; the left contained straw-colored fluid. The pericardial sac contained a slightly increased quantity of fluid.

The heart weighed 212 Gm. The epicardium was smooth and glistening. The musculature was flabby. Both auricles were dilated. The foramen ovale was patent. The mitral, pulmonary, tricuspid and aortic valves were normal. The musculature of the right ventricle measured 4 mm.; that of the left, from 9 to 11 mm. On section there were extensive areas of yellowish-gray, dense tissue scattered throughout both walls. The interventricular septum showed a similar appearance, the upper quarter being very thin and translucent. Large thrombotic masses adhered to the walls of the apexes of both ventricles. The coronary arteries appeared normal.

Microscopic sections showed extensive areas of destruction of cardiac musculature, with replacement by granulation and fibrous tissue, a picture similar to that seen in myomalacia and myofibrosis due to coronary occlusion. The coronary arteries, however, were normal, except that the terminal fine twigs contained organized thrombi. No spirochetes were found after prolonged search.

The other organs showed the usual changes found in chronic passive congestion.

DISCUSSION

ALFRED PLAUT: Might not the last case be an interstitial myocarditis? It happens, although very seldom, that a person dies in seemingly perfect health, and the autopsy shows nothing except a certain dilatation of the heart, and unless microscopic examination of the heart muscle is made, the case remains a mystery. The fact that the disease started after the accident with the football perhaps is entirely accidental.

As to the other case, I should like to know how far the bacteriologic examination of the autopsy material has been carried — whether any material was used

for cultures or animal inoculations. Perhaps that might have been one possibility of learning something of this widespread inflammation, and the fact that all the stains for bacteria were negative would possibly not exclude an infection with the pseudotuberculosis group, which are very difficult or impossible to stain in sections.

COLEMAN RABIN: The first case reminds me of a Negro woman on whom an autopsy was performed at the Mount Sinai Hospital. She had recently come from the West Indies, and entered the hospital with cardiac failure, dying soon thereafter of what appeared to be acute myocardial failure. At the postmortem examination there was found a dilated heart, which showed necrosis of muscle fibers, old fibrous tissue and fresh granulation tissue—a picture quite similar to the one shown in the slide. The clinical story was the same—acute cardiac failure in a patient who had apparently been perfectly well, and who showed at postmortem examination an old cardiac lesion of the type described by Dr. Lederer. Similar cases have been described of acute cardiac failure in beriberi; in these cases, coolies drop dead in their tracks, and post mortem an old lesion of the heart is found—a clinical and postmortem picture altogether similar to that in Dr. Lederer's case. I may suggest that although this is probably not beriberi, the diarrhea and hemorrhages are suggestive of a nutritional disturbance.

MAX LEDERER (closing the discussion): The diagnosis of interstitial myocarditis is very tempting in both of these cases. I think when one looks up the question of interstitial myocarditis, one usually finds that there is some etiologic factor to which the lesion can be traced. Those cases in which the myocardium alone is affected without known etiology and without other changes in the body are known as isolated myocarditis. The second case may possibly belong to that group. This boy was 13 years of age. He had been perfectly well until he was hit with the football. He was a big, strapping boy for his age. He had had pneumonia at 6, and he had evidences of old pleurisy. The lung was adherent, and there was no fluid on that side, whereas there was some on the other side. I thought that he had a myocardial condition that began at that time and continued until his heart failed. There was no acute lesion. The question of nutritional disturbance I think may be ruled out.

In the first case there was a question of nutritional disturbance for a long time, with the continued diarrhea. We did not make postmortem cultures or any experiment on animals. In our hospital the results with postmortem cultures are discouraging, because our material comes to us so long after death.

The question of beriberi was not gone into.

The strange thing is that the conditions in these hearts occurred in persons at such a young age: 21 months and 13 years. As I said in my opening remarks, I presented them mainly because of the fact that pathologists who had seen a great many hearts told me they had never seen any just like these.

A CASE OF ENDOCARDITIS DUE TO BACTERIUM ACIDI-LACTICI. LEWIS DICKAR.

This appears to be the first case of bacterial endocarditis due to B. acidi-lactici reported in the literature.

The micro-organism is considered to be a separate species in the B. coli group; others regard it as one of the varieties of B. coli. It resembles the other bacilli in this group, but is readily distinguished from them by its lack of power to ferment saccharose and salicin.

One other example of infection with B. acidi-lactici was reported by Ray in 1923—a case of meningitis in which the micro-organism was isolated from the blood and spinal fluid. Several cases of endocarditis due to B. coli are known.

History.—A man complained of frequency of micturition and nocturia. The only previous illness of interest was a mastoiditis with operation two and one-half years before. His present illness began abruptly two days before admission, with marked frequency of urination, nocturia and fever. The temperature was 102 F.; the pulse rate, 96; the respiration rate, 20; the blood pressure, 144 systolic and

60 diastolic. He was an obese man of 54, acutely ill. The chest and abdomen appeared to be normal. The heart sounds were of fair quality, and no murmurs were heard. The prostate was prominent, soft and tender. There was slight hematuria after the rectal examination.

The red blood count was 3,700,000 on admission and dropped to 3,000,000 shortly before death. The white count was 10,000 on admission. The urine showed the presence of albumin and diacetic acid on one occasion. White blood cells were always found.

The temperature rose to 106 F. on November 10. On November 15, an external urethrotomy with incision and drainage of a prostatic abscess was performed. Several drachms of pus was removed. No culture was taken. A blood culture on November 17 was positive, a gram-negative bacillus being isolated. The white count rose to 27,850, with 92 per cent polymorphonuclear leukocytes. A blood culture on November 26 was sterile. The temperature began to drop slowly until November 29, when it became septic. The white count at this time was 15,000, with 91 per cent polymorphonuclears. A blood culture on December 2 was positive. On December 3, a physical examination revealed dulness at the base of the right lung and râles at the base of the left lung. On December 4, bronchovesicular breathing was present on the left side. A loud systolic and a soft diastolic murmur were heard for the first time. These became louder from day to day. The pulmonary signs continued changing. On December 7, petechiae were found in the left conjunctiva, and the fingers on the right hand were painful. Petechiae appeared elsewhere; in addition, the right wrist became painful and swollen. On December 10, the patient was slightly irrational. The white count had again risen to 26,400, with 89 per cent polymorphonuclears. On December 11, the patient was exceedingly irrational; meningismus developed in the afternoon. That evening he suddenly became livid, and the pulse rate dropped to 48. He died thirty-five days after admission and twenty-seven days after operation.

The clinical diagnosis was subacute bacterial endocarditis due to B. acidi-lactici and abscess of the prostate.

Autopsy.—The autopsy was performed nine and one-half hours post mortem. There were many petechiae in both conjunctivae and in the skin of the trunk and upper extremities. The perineal incision was clean and not draining. The most striking findings were in the heart.

The heart weighed 500 Gm. The auricles were covered with thick, gray, firmly adherent membrane. Otherwise the right auricle was normal. The tricuspid valve was thin and delicate. At the base of the septal leaflet was a nodule about 0.5 cm. in diameter. On section an abscess was found, surrounded by a hemorrhagic area. The right ventricle was dilated and hypertrophied. The pulmonic valve was normal. In the left auricle was an elevated hemorrhagic area in the fossa ovalis. The mitral valve was slightly thickened at the line of closure. Several small hemorrhagic areas were present in the base of the valve. A hemorrhagic area about 3 mm. in diameter was present in the posterior papillary muscle. The left ventricle was hypertrophied and dilated. The aortic valve leaflets were covered with vegetations, which were soft, crumbly and pale yellow. The largest vegetation measured 2.5 cm. in length and 1.5 cm. in thickness, and entirely covered the right posterior leaflet. This leaflet was ulcerated, leaving an opening about 2 mm. in diameter. Extending from this were small masses, growing down over the endocardium of the left ventricle, the aortic leaflet of the mitral valve and to the base of the tricuspid valve through the muscle. The areas to which the vegetations were adherent were hemorrhagic. The myocardium was firm, with no visible fibrosis.

The coronary arteries were mildly sclerotic. The aorta had many small atheromatous plaques.

The lungs were voluminous and crepitant throughout. The spleen weighed 280 Gm. It was soft and reddish brown. On section the pulp bulged over the capsule. The corpuscles were large.

The liver weighed 3,320 Gm. and was normal.

The gallbladder was large and filled with thick, greenish-black bile. Two stones were present. The wall of the gallbladder was thickened.

The pancreas and the suprarenal glands were normal.

The kidneys each weighed 260 Gm. The capsule of the right kidney stripped easily, leaving a very finely granular surface, which was pale yellowish green with many small light yellow areas. On section the color was yellowish brown. The cortex was 8 mm. in thickness. Small abscess cavities filled with yellowish pus were present. Many tubules in the pyramids were seen as yellowish stripes. The left kidney had a more granular surface. It was yellowish brown, with small elevated yellowish areas. On section it was pale reddish brown. The cortex was thin, measuring 5 mm. in thickness. Red longitudinal stripings were present. The pyramids were made up of alternate stripes of red and yellow. In them were several large abscess cavities up to 1.5 cm. in diameter, filled with pus.

The bladder was thick-walled. The mucous membrane was pale.

The prostate was not enlarged. It was firm and asymmetric. The left side was larger than the right. The capsule was indistinct and merged with the periprostatic tissue. Many small pus-filled abscesses were present. The seminal vesicles and testes showed no changes.

The gastro-intestinal tract was normal.

The brain weighed 1,450 Gm. Externally, there was a hemorrhagic area on the parietal lobe of the right cerebral hemisphere close to the midline. On section many small pale red areas were found scattered through the cerebral hemispheres, internal capsules, cerebellar hemispheres and medulla. The spinal cord was not removed.

B. acidi-lactici was obtained in pure culture from the cardiac blood.

Microscopic Examination.—In the myocardium were areas of polymorphonuclear infiltration. Plugs made up of short fat rods filled many of the blood vessels. A section of the myocardium taken from a point near the aortic valve showed thickening of the endocardium and subendocardial layers. Parts of these structures were infiltrated with red blood cells and polymorphonuclear leukocytes, and then were replaced by a mass of fibrin containing many polymorphonuclear leukocytes, bacilli and necrotic débris. The necrosis extended into the myocardium with the formation of an abscess. The muscle fibers around this area were necrotic and disintegrated. A methylene blue (methylthionine chloride, U. S. P.) section showed the presence of many bacilli.

The entire aortic valve leaflet taken for microscopic study was necrotic. The surface was covered with vegetations containing large masses of bacteria, polymorphonuclear leukocytes and nuclear débris. The micro-organism was found to be a gram-negative bacillus.

The aorta showed the changes of moderate arteriosclerosis.

The sections of the lungs were normal.

The liver was normal in structure. The portal areas were cellular and contained polymorphonuclears. The sinuses were congested. In many areas masses of bacteria were also present. Many polymorphonuclear leukocytes were found, which were most numerous in the periportal fields.

The gallbladder was thick-walled. The submucous layer was congested and infiltrated by plasma cells.

In the pancreas, polymorphonuclear leukocytes were increased in numbers in a few areas where the acini were shrunken or disintegrated.

The lipoid material in the suprarenal gland was diminished. Bacterial plugs were found in several blood vessels.

Several sections of the kidney showed abscess cavities of varying size in the cortex and medulla. Areas of round cell infiltration were present. Bacterial plugs were found in several glomerular tufts.

The acini of the prostate contained desquamated cells and débris. In a few, necrotic material and polymorphonuclear leukocytes were found. The stroma

was infiltrated with round cells. In another section several abscesses were found. Dense round cell and plasma cell infiltrations were present in the stroma. Many bacilli were present in the sections stained with methylene blue.

The tubules of the testes had thickened basement membranes. Several blood vessels were present, with the walls and surrounding tissue infiltrated with polymorphonuclear leukocytes, round cells and plasma cells.

Several sections of the cerebrum were examined. In one localized area, the meninges were infiltrated by many polymorphonuclears and round cells. Bacterial plugs occluded several blood vessels in the substance of the brain. About these vessels were polymorphonuclears and round cells, which for the most part were sharply perivascular; in only one area in the cerebrum was the brain itself involved.

Anatomic Diagnosis.—The anatomic diagnosis was: chronic and acute prostatitis with abscess; external urethrotomy, with perineal incision and drainage of the prostatic abscess; cystitis cystica; acute bacterial endocarditis (B. acidi-lactici) of the aortic valve, with extension to the mitral and tricuspid valves; bacteremia (B. acidi-lactici), with metastases in the myocardium, pancreas, liver, kidneys, testes, brain and leptomeninges; acute splenic tumor; chronic cholecystitis, and cholelithiasis.

Comment.—The original focus of infection in this case was most probably the prostate gland. The portal of entry in most cases of sepsis due to B. coli is the urinary tract. Invasion of the blood follows cystoscopy or surgical trauma. This patient showed no signs of involvement of the heart when he entered the hospital. Following the operation there was invasion of the blood with localization of bacilli on the aortic valve leaflets.

DISCUSSION

GEORGE CAHILL (by invitation): This patient had an abscess that localized back of the right side of the prostate. Two years previously he had had a mastoiditis requiring two radical operations within three weeks. I had a suspicion that the prostatic abscess was secondary to the mastoiditis, because two years ago a similar case was seen in which, on opening and draining, Friedländer's pneumobacillus was present in the pus and blood stream, as proved on culture. The patient proved clinically to have a "feeder" in the right jugular vein. At first cultures in the present case showed a gram-negative bacillus with a capsule, and naturally it was suspected of being a pneumobacillus. The bacteriologic department, however, on culture showed that the infecting organism was B. acidi-lactici. However, clinically, I still think that the prostatic abscess was metastatic. Although no blood culture was taken before the operation, on reviewing the case, I considered that the patient then must have had bacteria. The abscesses in the kidneys were without any local symptoms. This is a common observation in genito-urinary cases. I hoped that the mastoid might show some infection, because the x-ray film showed some cells still in the mastoid, but clinically it was silent. This, in view of the former case, was an interesting point, because from a history obtained from the family later on, the illness apparently had started several weeks before the patient admitted that he was ill.

BARTONELLA MURIS ANEMIA: IV. PATHOLOGIC CHANGES DURING THE ACUTE ANEMIA. DAVID PERLA and (by invitation) J. MARMORSTON-GOTTESMAN.

The pathologic changes that follow a severe infection with Bartonella muris and the associated anemia in the adult or young albino rat are: first, the changes that are stimulated by the release of large quantities of cellular débris into the circulating blood, phagocytic activity and hyperplasia of the endothelial elements of the liver, thymus and lymph nodes, and in the young rat, of the spleen, with resultant capillary thromboses and focal necroses; second, those changes resulting from the anemia: fatty metamorphosis of the heart, liver and kidneys. A third element is a severe nephrosis, with, in some instances, a degenerative process in the glomeruli. In the bone marrow, hyperplasia of the erythropoietic elements occurs.

BARTONELLA MURIS ANEMIA: V. COMPENSATORY PHENOMENA FOLLOWING SPLENECTOMY IN THE ADULT ALBINO RAT. J. MARMORSTON-GOTTESMAN (by invitation) and DAVID PERLA.

In Bartonella muris carrier stock following splenectomy and recovery from the anemia, certain changes are observed in the lymphoblastic and reticular and endothelial elements of the body. These changes appear from three to five months after splenectomy and are associated with immunity to further infection with Bartonella muris. The changes consist primarily of hyperplasia of the hemolymph tissue, hyperplasia of the reticular and endothelial elements of the lymph nodes, the formation of lymphoblastic foci periportally in the liver and peribronchially and perivascularly in the lung, regeneration of all elements of the thymus and marked hyperplasia of all elements of the bone marrow (increased hematopoiesis).

COMMENT

MENDEL JACOBI. In the experimental production of amyloid in mice on which we reported at the meeting of another society, the lesions we found preceding the development of adult amyloid resembled almost identically those which Dr. Gottesman presented. I should like to ask if in their rats there was any suggestion, either grossly or histologically, that might lead them to suspect that they had some amyloid.

DAVID PERLA: There was not a trace of amyloid; nothing to suggest it grossly or microscopically.

MENDEL JACOBI: Have you used the congo red specific stain for amyloid?

DAVID PERLA: No, there was no suggestion of amyloid.

MENDEL JACOBI: We have found that, even when there was no gross or microscopic suggestion of amyloid, with the specific stain for it, it could be demonstrated.

DAVID PERLA: Where would you suggest that we look for it ?

MENDEL JACOBI: In the reticulo-endothelial cells.

DAVID PERLA: I personally should not place much confidence in such a finding, and I should be dubious if we could prove by a specific stain that there was amyloid deposited in the cells, when there was no gross or microscopic evidence of it.

Regular Meeting, May 28, 1931

LEILA CHARLTON KNOX, *President, in the Chair*

A CASE OF FOREIGN BODY IN THE ORBIT. REUBEN GOODMAN.

The cases reported in the literature may be divided into two groups: (1) cases of long duration, including (*a*) those unaccompanied by discomfort or symptoms, (*b*) those presenting symptoms after a variable period and in which removal of the foreign body gives satisfactory results, and (*c*) those in which removal is followed by unsatisfactory results; (2) cases of short duration, including (*a*) those without ill effects and (*b*) those with ill effects. The following case is presented because of the interesting history and unfortunate outcome.

A boy, aged 2, was admitted, on March 18, 1931, to the Jewish Hospital of Brooklyn with a history of a fever of 104 F., and prostration for two days. The family and past histories were irrelevant. One week previously, the patient accidentally lacerated his left upper eyelid with a sharpened end of a lead pencil. He

was taken to a hospital, where the wound was sutured with one stitch, and he was given two injections of tetanus antitoxin. He was apparently well until three days before admission; then he became irritable and listless. The temperature rose to 102 F. The day before admission, he vomited several times. The vomiting was projectile. He rolled his head and eyes from side to side, resented being touched, and would "shiver" all over, as though convulsed, on being handled. On the morning of admission the child became comatose, and the temperature rose to 105 F.

Physical examination showed the child to be well developed and well nourished, acutely ill and comatose. There was proptosis of the left eye. The jaws were held clenched, but could be opened. The patient ground his teeth frequently and was foaming at the mouth. The skin, lymphatic system and head were normal. Both eyes were somewhat chemotic; the blood vessels were full. Both eyes were fixed, and there was an optic neuritis bilaterally, more marked on the left. The disks were swollen and their outlines blurred. The veins were full and interrupted. The nose and ears were normal. The tongue was swollen from biting. The pharynx was markedly injected. The neck was slightly rigid. The chest, heart and lungs were normal. The abdomen was distended. The extremities showed spasticity, more marked on the right. The deep reflexes were hyperactive, more so on the right. Abdominal reflexes were not elicited. The Babinski sign was positive bilaterally.

The blood count showed 29,600 leukocytes, of which 75 per cent were polymorphonuclears, 22 per cent lymphocytes and 3 per cent mononuclears.

The spinal fluid was removed under slightly increased pressure; it was slightly cloudy and contained 200 cells per cubic millimeter, 85 per cent of which were lymphocytes. Gram-positive diplococci were seen on direct smear. The globulin was ++, and Fehling's solution was reduced.

The spinal fluid removed four hours later contained 4,900,000 cells per cubic millimeter, 90 per cent being polymorphonuclears.

The patient did not respond to treatment, but died on the day of admission. The clinical impression was that of cavernous sinus thrombosis, left orbital cellulitis, meningitis and acute pharyngitis.

Postmortem examination showed that the left eyeball was normal. On removing the calvarium, the epidural surface was normal. The meningeal vessels were congested. The brain was edematous. The subarachnoid of the anterior and inferior surface of the left temporal lobe contained thick, yellow-green, creamy pus in a tract about 4 cm. wide. This could be traced to the cerebral surface of the frontal lobe, where there was a large collection of pus. On the adjacent right hemisphere, a similar but less abundant exudate was seen. In the center of the inferior surface of the left frontal lobe was a mass of granulation tissue about 1 cm. in diameter, from which thick, yellow-gray pus exuded on pressure. No pus was found at the base of the brain. On the orbital plate of the left frontal bone, immediately beneath the granulation tissue described, was a defect about 5 mm. in diameter, surrounded by a few fragments of bone, the result of perforation. The dura mater covering this area was congested, and on its superior surface there was about 2 cc. of thick, gray-yellow pus. On removal of the dura, pus could be expressed through the orbital opening by pressure on the eyeball. Immediately beneath the perforation, in the orbital fat, was a small abscess containing fluid pus; lodged just beneath the fracture were fragments of pencil and a piece of lead.

DISCUSSION

MAX LEDERER: There are some points to be emphasized here. First, only a very close examination of the left eyelid disclosed a scar. Apparently the wound had healed by primary union, and there was certainly no infection of the tissues of the eyelid. Second, the specimen being shown does not represent the actual picture, because in trying to fix the end of the pencil in the soft tissues, the fragments of bone were dislodged and lost. Where there is now a hole in the

orbital plate, that place was occupied by fragments of the bone. Third, from a practical standpoint, Dr. Goodman did not mention that there was a laceration of the inferior surface of the frontal lobe, where the point of the pencil had lacerated the brain tissue as well, which later became the site of the superficial abscess.

This case also emphasizes the necessity in all these instances of making a roentgen examination of the skull or orbit. The patient was first seen in the hospital to which he had immediately been taken; the wound was then sutured and the child discharged, with the sequelae that have been demonstrated.

OSTEOGENIC SARCOMA-LIKE TUMOR OF THE METACARPAL BONE. HENRY L. JAFFE and (by invitation) LEO MAYER.

A tumor of the fourth metacarpal bone was described. It began when the patient, a girl, was 12 years of age. After growing slowly for almost three years, it began to grow rapidly. The tumor mass was removed; it measured 10 by 6.5 by 6 cm. Only the articular head of the metacarpal remained. The tumor was of such consistency that it could be cut with a knife, but it was quite granular and firm. Histologically it showed a marked production of osteoid tissue and also the formation of trabeculae of normal, new-formed bone. The osteoid tissue arose from cells that had many of the features of osteoblasts. The tumor has not recurred one and a half years after operation, though the histologic appearance suggests on casual examination the diagnosis of osteogenic sarcoma. It is believed that this tumor is an osteoblastic, osteoid-forming tumor of slow growth, and that the prognosis is good. It is therefore related to the osteoid chondroma of Virchow.

DISCUSSION

PAUL KLEMPERER: This is a very unusual type of tumor and has many interesting points. I should like to say that I admire the courage of Dr. Jaffe, for calling this tumor from the very first nonmalignant. I think that most of us would have made the diagnosis of a malignant osteogenic sarcoma. If I understood Dr. Jaffe correctly, there was one point that caused him to consider this tumor nonmalignant, from the histologic aspect, and that was the presence of the osteoblasts. I think one is struck by the uniformity of the cell type, which coincides very well with the osteoblasts of the normal bone, and this may be then actually a differential point that might help in future cases to give a better prognosis than one would if one should call this tumor an osteogenic sarcoma. That it is an osteogenic tumor I think Dr. Jaffe does not doubt. It originates in the mesenchyme of the bone, and this cellular structure and intercellular substance are found only in bone.

The question arises whether tumors of the osseous mesenchyme, which have such a definite maturation, like the production of osteoblasts, are less malignant than other tumors. Some years ago I saw a tumor in certain respects similar to this, in which the cell type was such that I could only identify it with the osteoblasts, and here also the uniformity of the cell type was very striking. In this case it was not a tumor of a short bone, but of the humerus. The end-result was similar to that in this case. It occurred in a boy of 15 years, who three and a half years ago was operated on because of the tumor in the head of the humerus. Only the tumor was resected. No radical operation was performed, the tumor being excised with a wide margin. The histologic picture was that of a very cellular tumor with one cell type predominating. This patient is today in perfect health and has no metastases.

Can Dr. Jaffe tell us how long one can expect metastases from an osteogenic sarcoma after removal of the tumor—whether there is sometimes a very long latent period or not? As far as I recall, I think usually the period is short, and that metastases appear very shortly after the onset of the disease. In this case of four years' duration, is it correct to assume that no metastases will occur?

Furthermore, I would like to know whether what we used to call osteoid sarcoma might not be the same type of tumor. I believe that osteoid sarcoma was generally considered not as malignant as osteochondrosarcoma, so this question has to be asked in order to classify this tumor properly. It might be identical with the osteoid sarcoma of old and remarkable mainly on account of its peculiar localization.

FRANCIS CARTER WOOD: I have seen a tumor of the antrum which in some ways resembled what Dr. Jaffe has shown. It was submitted to the members of the Codman Committee, most of whom believed it benign. The growth filled the antrum and was resected as a sarcoma. I made the diagnosis of sarcoma, but the patient is still well.

HENRY L. JAFFE (closing): I am of the same opinion concerning osteogenic sarcoma as Dr. Klemperer—that it generally metastasizes quickly; four and a half years is a long time. I think that we may now expect this girl to make a complete recovery.

I am not certain that I know definitely what the osteoid sarcoma of Virchow is. It is difficult to decide from what is described in the old literature. These tumors are described as containing cartilage, and others describe lesions resembling periostitis. I have had specimens of osteoperiostitis sent in suspected of being Virchow's osteoid tumor, which of course they are not.

I believe that the thing of practical importance in connection with osteoblastic tumors of the hands and feet is the question of amputation. I am not considering bones such as the os calcis. I have been unable to find in the literature cases that have been followed for any period of time. Aside from the two cases described by Bergstrand, Handl described two cases in 1906. These were reported shortly after removal of the tumors, and his report is not accompanied by photographs or drawings, and this makes it difficult to judge independently what he was dealing with. Buffalini, some years later, described a tumor that seems to have arisen from a metacarpal bone. This was possibly of the mixed cell type, but it was also described very shortly after removal.

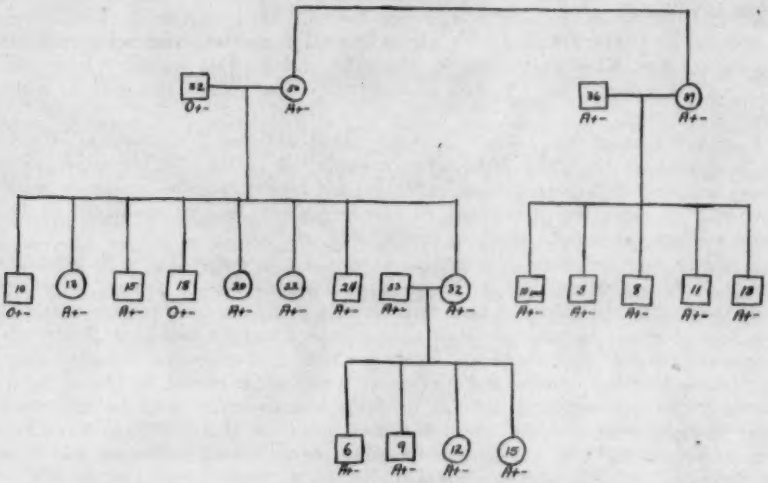
HEREDITY OF THE AGGLUTINOGENS M AND N OF LANDSTEINER AND LEVINE, WITH PARTICULAR REFERENCE TO THE DETERMINATION OF PATERNITY. ALEXANDER S. WIENER AND MAX LEDERER.

By means of immune rabbit agglutinins, Landsteiner and Levine have demonstrated the existence in human red blood cells of several agglutinogens, designated by them as M, N and P, that are independent of the agglutinogens A and B, and have succeeded in dividing all human blood into at least thirty-six distinct types. Of the newer agglutinogens, Landsteiner and Levine studied the two agglutinogens M and N in greater detail, and these agglutinogens are the subject of this paper.

Landsteiner and Levine have demonstrated that the agglutinogens M and N are inherited as mendelian dominants and have also proposed a theory according to which the inheritance of these agglutinogens depends on a single pair of allelomorphic genes, M and N, located in a certain pair of chromosomes. Any person could therefore have in that pair of chromosomes any one of the following combinations of genes: MM, MN or NN. And, corresponding to the genotypes, MM, MN and NN, we have three phenotypes, termed by Landsteiner and Levine M + N —, M + N + and M — N +, respectively. The theory, therefore, accounts for the nonexistence of the type M — N —. On the basis of this theory, the expected values for the types of offspring are: from cross M + N + by M + N +, M + N + 50 per cent, M + N — 25 per cent and M — N + 25 per cent; from cross M + N + by M — N +, M + N + 50 per cent and M — N + 50 per cent; from cross M + N + by M + N —, M + N + 50 per cent and M + N — 50 per cent; from cross M + N — by M — N +, M + N + 100 per cent; from cross M + N — by M + N —, M + N — 100 per cent, and from cross M — N + by M — N +, M — N + 100 per cent.

The results of a study of 131 families with 642 children are shown in table 1. Two apparent exceptions to the theory of Landsteiner and Levine were found. In one family, the father and mother were both of type M + N —, but one of the children was of type M + N +. In another family, the father belonged to type M — N +, the mother to type M + N +, and one of the children to type M + N —. In both cases there is a possibility of illegitimacy, however, especially in considering the fact that as many as 642 children were examined in this study.

The same families that were examined for M and N were also examined for the heredity of the agglutinogens A and B. There was one apparent exception



Ross-Jagofsky-Shapiro family.

TABLE 1.—*Heredity of Agglutinogens M and N of Landsteiner and Levine*

Types of Parents	Number of Families	Children of Types			
		M+ N+	M+ N—	M— N+	Totals
M+ N+ × M+ N+	25	58	29	29	116
M+ N+ × M— N+	36	83	1*	92	176
M+ N+ × M+ N—	43	119	97	0	216
M+ N— × M— N+	10	46	0	0	46
M+ N— × M+ N—	14	1*	68	0	69
M— N+ × M— N+	3	0	0	19	19
Totals.....	131	307	195	140	642

* A question of illegitimacy arises here.

to the Bernstein theory of heredity of the Landsteiner blood groups, namely, a family in which the father belonged to group AB, the mother to group B and one of the children to group O. Since the exception here is on the paternal side, the possibility of illegitimacy cannot be excluded. Our study, therefore, produced additional evidence in favor of the Bernstein theory.

One of the families examined was studied into the third generation. The result of this study is shown in the accompanying diagram. The family consisted of 22 persons living in one large three-family house. The remarkable observation was that of these 22 persons living in one house, 19 were of type A + — and three of type O + —. Thus, of 22 persons, 19 belonged to one type and 3 to

another. Furthermore, von Dungern and Hirzfeld in 1910 demonstrated the existence of two different subgroups of group A cells, which have been designated as A_1 and A_2 by Landsteiner and Levine, of which A_1 is the more frequent subgroup. The 19 group A persons in the Ross-Jagofsky-Shapiro family belonged to subgroup A_1.

The results of this study, with the results published by Landsteiner and Levine, and by Schiff, indicate, as has already been pointed out by Landsteiner and Levine, that the agglutinogens M and N can be used medicolegally for the determination of nonpaternity, as is shown in table 2.

It is of interest to know how frequently nonpaternity can be proved when the putative father is not the true father. It has been calculated that in one sixth of such cases, nonpaternity can be proved by means of agglutinogens M and N alone. This is equal to the chances of proving nonpaternity by means of agglutinogens A and B, so that the discovery of Landsteiner and Levine has doubled the number of cases of questioned paternity that can be solved.

TABLE 2.—*Heredity of the Agglutinogens of M and N of Landsteiner and Levine*

Types of Parents	Types of Children Possible	Types of Children Not Possible
M+ N+ × M+ N+	M+ N+, M+ N−, M− N+	
M+ N+ × M− N+	M+ N+, M− N+	M+ N−
M+ N+ × M+ N−	M+ N+, M+ N−	M− N+
M+ N− × M− N+	M+ N+	M+ N−, M− N+
M+ N− × M+ N−	M+ N−	M+ N+, M− N+
M− N+ × M− N+	M− N+	M+ N+, M+ N−

The new-found agglutinogens can also be used in cases in which new-born infants have been accidentally interchanged, as happened in a recent case in Chicago. Fully two thirds of such cases can be solved by the combined use of the agglutinogens A, B, M and N.

DISCUSSION

MAX LEDERER: I should like to emphasize, as I did about a year ago, the medicolegal importance of this work, which apparently has not been recognized in this country. In Germany, Norway, Switzerland and Denmark this method of testing has been accepted in the courts in cases in which there exists illegitimacy, and the courts have made it mandatory that these tests shall be done before the trial takes place, the reasons being twofold: first, it saves the government the expense of conducting a trial, and second, it prevents perjury. The latest statistics on the subject that I have been able to collect show that now there have been tests in 5,512 cases in the German courts with the old grouping method, but not with the M and N method, and in about 448 cases it was shown definitely that the accused person could not be the father of the child. That is quite a large number of cases, and certainly testifies to the importance of the method.

In a recent case, the question was put to Dr. Wiener, whether the husband or a second man was the father of a child. As both men belonged to group A, the Landsteiner blood groups did not help solve the problem. By examination of the bloods for M and N factors of the mother, the child and the two men, the second man could be excluded as father of the child, and the legitimacy of the child was thus established.

There was also an application of this test in cases of murder. I need not go over the details here. It is indeed surprising that this country, progressive as it is in medical work, should so far have done nothing to apply these tests medicolegally. The A and B method alone has been used in a few instances, as in the Chicago case. However, there are any number of cases that occur in large cities, in which it is necessary for the corporation counsel to obtain all the information possible in order to decide whether a given man is the father of a

child or not, and if one takes into consideration the saving of the expense of the numerous trials that take place for this purpose, it certainly seems worth while to incorporate this test into our medicolegal procedures.

SILIK H. POLAYES: From the point of view of transfusions, although there are no normal agglutinins for the agglutinogens M and N, it is possible that the same thing that happens in rabbit's blood may happen in human blood, if the recipient who does not possess these agglutinogens receives blood from a person whose blood contains either of them. In other words, the first transfusion may stimulate the production of agglutinins specific to agglutinogens M and N, so that on subsequent transfusions it seems possible for a reaction to occur between the newly developed agglutinins and the foreign agglutinogens M and N.

ALEXANDER S. WIENER (closing the discussion): I might add that there are two subgroups of A, namely, A_1 and A_2, and in addition the agglutinogen P which I mentioned. The heredity of these agglutinogens has also been studied; they are definitely inherited, but because of the technical difficulty in testing for these substances, the heredity is not perfectly worked out yet, and the time is not ripe for their medicolegal application. The possibility remains that by the immunization of animals besides rabbits with human blood, more and more agglutinogens may be discovered as time goes on, so that the percentage of cases of nonpaternity proved without the aid of any evidence but the examination of the bloods, instead of being 33, may be increased to 50 or 75, or perhaps at some time to the ideal of 100 per cent. Furthermore, with just the agglutinogens that I have mentioned, namely, A_1, A_2, B, M, N and P, we can distinguish thirty-six different types of human blood. Therefore, in a medicolegal case, in which a question of the identification of a blood stain arises, when the blood stain might belong to one of two persons, the chances of the two persons belonging to the same one of the thirty-six types are very small, so that the chances of identifying blood stains in such cases are good.

LESIONS OF THE BRAIN IN INFLUENZA. IRVING J. SANDS (by invitation).

Nervous and mental complications are quite common in influenza. They are essentially due to changes occurring in the nervous system. The brain changes in the 1889-1891 epidemic have been described in the literature as "hemorrhagic encephalitis." The epidemic of 1917-1919 was so intimately associated with epidemic encephalitis that all the lesions of the brain occurring in that epidemic of influenza have been described under the heading of epidemic encephalitis. Four cases occurring in the recent epidemic of influenza have been examined post mortem at the Jewish Hospital of Brooklyn and studied anatomically. There is no doubt of their being cases of influenza.

Grossly, the brains appeared reddened and congested, and the veins were distended with blood. There were numerous small punctate pial hemorrhages present. The dura apparently was normal. The pia was congested and showed infiltration with lymphocytes, plasma cells and a few polymorphonuclear cells. The pial vessels were engorged with blood. The nerve cells showed marked cloudy swelling, chromatolysis, satellitosis and neuronophagia. There were numerous areas where there was a great loss of nerve cells, and the latter were replaced with glia cells. The blood vessels showed inflammatory changes, the Virchow-Robin spaces being filled with lymphocytes and plasma cells. There were numerous areas where there was considerable blood around these vessels. The changes were most marked in the region of the third ventricle and in the corpus striatum. In one case there was an extensive subarachnoid hemorrhage, caused apparently by a massive cerebral hemorrhage. The changes were also found in the white matter. In one case, the chief seat of pathologic alteration was in the medulla.

Case 1 was that of a girl of 14 months, who became ill with a cough and running nose, and two days later was admitted to the hospital. She was cyanotic and dyspneic and appeared toxic. She showed signs of congestion in the base of the left lung and leukopenia. Death occurred three hours after admission.

Postmortem examination showed the characteristic red and congested condition of the pharynx, larynx, trachea and bronchi. The lungs showed hemorrhagic areas, and there was considerable hemorrhage in the alveoli. A purulent process was found in the bronchi. There were numerous abscesses in the lungs. There were petechial hemorrhages in the kidneys. The brain showed the changes described.

Case 2 was that of a man complaining of abdominal pain on admission to the hospital. He showed general arteriosclerosis and an icteric tinge to the skin. He lapsed into coma and died a day after admission. Postmortem examination showed the reddened condition of the respiratory tract and the hemorrhagic condition in the lungs. Coronary sclerosis, chronic cholelithiasis and myofibrosis cordis were found. The brain showed the changes described, and there was a moderate subarachnoid hemorrhage over the parietal lobe.

In case 3, a high temperature and respiratory difficulty suddenly developed in a girl of 4 months. On admission to the hospital, she had two general convulsions. There was dulness at the bases of both lungs. Death occurred two days after the onset of the illness. Postmortem examination again showed the typical changes in the larynx, pharynx, trachea and bronchi. The lungs showed edema and congestion, and hemorrhagic exudate in the alveoli. The brain showed the changes described. There was a large subdural clot in the left middle fossa.

Case 4 was that of a 48 year old woman, who had nursed four members of her family in influenza. She suddenly complained of weakness and headache. The following day she went to bed and became drowsy. The next day she showed marked rigidity of the neck, depressed deep reflexes, slow pulse and a temperature of 101 F. The diagnosis of subarachnoid hemorrhage was made, and on admission to the hospital a bloody spinal fluid confirmed the diagnosis. She lapsed into deep coma and died two hours after admission. Postmortem examination disclosed a congested, hemorrhagic condition of the trachea, bronchi and lungs. There was marked subarachnoid hemorrhage, covering the entire right hemisphere, more marked at the anterior two-thirds, and there was a similar, though lesser, hemorrhage on the left side. The great cisterns were filled with blood. There was a massive cerebral hemorrhage, measuring 3 by 4 by 5 cm., in the left frontal lobe, which communicated with the subarachnoid space, but which did not communicate with the ventricles. The rest of the brain showed the changes described.

The cause of influenza is unknown. There are many who believe that the Pfeiffer bacillus is responsible. There are others who maintain that it has nothing to do with influenza. The cause of epidemic encephalitis is unknown. Many maintain that it is caused by a filtrable virus; some claim that it is due to a streptococcus, and many believe that it is caused by a toxin the organisms producing which are situated in some other part of the body. Many are convinced that there is a close relationship between influenza and epidemic encephalitis. There is a group of observers who believe that it is caused by the same noxious agent. The relationship between epidemic encephalitis and influenza is still a subject of great controversy and speculation.

DISCUSSION

MAX LEDERER: One of the most difficult things in evaluating the information obtained is the primary diagnosis. Are we dealing with influenza or not? This difficulty of diagnosis was very well emphasized during the recent epidemic of influenza. There are those of us who have had the fortunate experience (from our standpoint) of performing autopsies in quite a number of cases of influenza during the epidemic of 1918-1919, and we were thoroughly impressed with the pictures those cases presented, and those who have not seen material of that type are skeptical as to whether we are dealing with the same condition now. In the beginning of this last epidemic I began to watch for these cases; we performed autopsies in about fourteen, in all of which was shown the one outstanding sign on which I place a great deal of importance, namely, the intense reddening of

the trachea and the bronchi, and perhaps the larynx as well, with ulceration and hemorrhage, occasionally accompanied by a dark green, shaggy membrane. Of course, the other respiratory lesions that occurred were not so constant, and I suspect that they were not so constant because of the superimposed processes that occurred, such as empyematous abscesses due to staphylococci particularly, and in some instances in which the lesion in the upper part of the lung was relatively mild the patients died of something else, or as in this one case, of a hemorrhage in the brain. In this case Dr. Sands told the story as it occurred as far as the patient was concerned from the standpoint of the history of the disease, but not from that of the diagnosis. The latter was made at the autopsy table, and Dr. Sands went back and obtained the story later on, that the patient had been nursing patients with influenza. We originally suspected that she had been suffering from a fracture of the skull, which made it a medical examiner's case.

After we had seen these fourteen or fifteen cases, I had my colleagues observe the pulmonary cases from a different point of view, and we were able to point out regularly, after the epidemic was over, that there was no reddening of the trachea, or very little, and I was able to convince most of my colleagues that the earlier cases belonged to the influenza group. They are being studied now for further report.

The lesions of the brain are of great interest, and Dr. Sands brings up the important point of the relationship of encephalitis to influenza, which is very suggestive, since after the 1918 epidemic of influenza the epidemic of encephalitis followed so promptly.

MAX TRUBEK: Was the possibility of traumatic cerebral hemorrhage thought of to explain the lesions in the last case? The multiple punctate cerebral hemorrhages appear not unlike those sometimes occurring after cranial injury, often without fracture of the skull. This probability came to mind even before the discussion showed that the fall with possible fracture of the skull was considered as a cause of death, before the autopsy.

IRVING SANDS (closing the discussion): The picture is entirely different. We find multiple punctate hemorrhages in traumatic encephalopathies, but we do not find any inflammatory areas around the capillaries. We do not see lymphocytic or plasma cell infiltration. That is the outstanding difference. Moreover, there are not found the typical toxic changes in the nerve cells.

Book Reviews

THE RENAL LESION IN BRIGHT'S DISEASE. By THOMAS ADDIS, Professor of Medicine, Stanford University Medical School, San Francisco, and JEAN OLIVER, Professor of Pathology, The Long Island College of Medicine, Brooklyn; Formerly Professor of Pathology, Stanford University, San Francisco. Cloth. Price, $16 net. Pp. 650, with 160 full page illustrations, 21 text illustrations and a large folding table. New York: Paul B. Hoeber, Inc., 1931.

This elaborate monograph presents in detail the results of a thorough, well considered study, extending over many years under the same general conditions, of the correlation between certain clinical phenomena and the anatomic changes in the kidneys in Bright's disease. As indicated by the title, only the renal lesions of Bright's disease are considered. By Bright's disease the authors mean bilateral, nonsuppurative renal disease associated with proteinuria. Their immediate problem was to determine the relations between the changes in the urine and the structural changes in the kidneys. Following the introductory chapter are three chapters dealing with the clinical methods used in the investigation, clinical definitions and a clinical classification. Probably never before has the urine of a series of cases of Bright's disease been studied so fully and in such detail with standardized quantitative methods as in this investigation. The next two chapters describe the methods and definitions employed in the study of the kidneys. Chapter 7, by far the longest, discusses the results of the clinical and anatomic observations of seventy-two cases of Bright's disease by the methods described. Two large photomicrographs, $\times 25$ and $\times 125$, illustrate the renal lesion in each case. A folding chart in a pocket on the inside of the first cover page gives a summary of the results in each case. Then follow chapters on comparison and correlation of the results of the clinical and structural observations, on the theoretical description of the course and sequence of the morbid processes in Bright's disease and on a classification and theory of Bright's disease. On the basis of correspondence between the urinary changes and the structural changes in the kidneys, the following classification of Bright's disease is set up: hemorrhagic, degenerative and arteriosclerotic. These terms are regarded now as self-explanatory. Generally speaking, these forms of Bright's disease can be recognized clinically by the results of proper examination of the urine. One is impressed with the complete grasp of the problems involved and with the thoroughness and objectiveness of the observations and the soundness of the interpretations.

The illustrations are excellent. The book is printed on heavy paper with wide spacing. It weighs more than 2,700 Gm. (6 pounds +), and the question as to whether this is the best form of book for the purpose comes up. "Fitness to its subject is the first quality of a wellmade book." However this question may be answered, the great scientific value of the contents recorded will not be affected. What next of Bright's disease? Experiment. "The correlation of function and anatomical structure which has not been touched on in this discussion at all, and which is the basic and all important part of the problem, is still a complete mystery. It is by experimentation, under controlled and simplified conditions, that this ultimate phase must be attacked. And it is from such endeavor . . . that a more satisfactory theory and classification of Bright's disease will eventually evolve."

TEXT-BOOK OF PATHOLOGY. By ROBERT MUIR, M.A., M.D., Sc.D., LL.D., F.R.S., Professor of Pathology, University of Glasgow, Pathologist of the Western Infirmary, Glasgow. Second edition. Price, $14. Pp. 872, with 501 illustrations. New York: Longmans, Green & Company, 1931.

This is the second revised edition of a textbook that first appeared in 1924. The value of the work is attested by the six printings through which the first edition has since gone. In the one volume, general and systemic pathology are discussed, but, as the author states in the preface to the first edition, these terms

are not used as it seemed inadvisable in a book of this nature to draw any sharp distinctions. The chapter on inflammation is especially clear and lucid, and it is well illustrated with many excellent reproductions. It is interesting that in classifying tumors, the groups histioma and cytoma, rather unusual terms in the American literature, are frequently used. In the chapter dealing with the brain, one finds its tumors classified as fibro-endotheliomas or meningiomas, neurofibromas and gliomas. Although the terms ganglioma and neuro-epithelioma are mentioned, no subdivision of the tumors of the glioma group is given. However, in an earlier general chapter on tumor, there is a discussion of the various tumors of the glioma group. The presentation of electrocardiographic tracings in the chapter on the heart conveys to the student the conception of applied cardiac pathology. This discussion is somewhat more detailed and broader in scope than that usually found in textbooks of pathology. Fibrosis of the myocardium and inflammatory changes are strictly differentiated. It is interesting to note that syphilis, with the exception of gummatous lesions, is classified among the fibroses and not as an inflammation. In many instances throughout the book reference is made to the disturbances of function as well as to the morphologic changes in the various pathologic states.

There are 501 illustrations. The histologic pictures, in general, are excellent; but some of the gross pictures are not as clear and instructive as might be desired. Only very few references are given that refer to larger contributions on the respective subjects. In summarizing, the book is not only a valuable aid for the medical student but also for the pathologist, who will find in it a great deal of information concerning modern nomenclature and conceptions of disease.

A Text-Book of Pathology. By Francis Delafield, M.D., LL.D., Sometime Professor of the Practice of Medicine, College of Physicians and Surgeons, Columbia University, New York, and T. Mitchell Prudden, M.D., LL.D., Sometime Professor of Pathology, College of Physicians and Surgeons, Columbia University, New York. Fifteenth edition. Revised by Francis Carter Wood, M.D., Director of the Pathological Department, St. Luke's Hospital, New York; Director of the Institute of Cancer Research, Columbia University, New York. Price, $10 net. Pp. 1,339, with 20 full-page plates and 830 illustrations in black and in colors. New York: William Wood & Company, 1931.

A brief history of this book is given in connection with the notice of the thirteenth edition (Arch. Path. **1**:496, 1926). The first edition was published in 1872 as a "Hand-Book of Postmortem Examination and Morbid Anatomy," by Francis Delafield. Hence the book is about to complete the unique record of fifty years of usefulness. At least since 1901, its avowed purpose has been to meet the need of medical students and physicians for a comprehensive, if of necessity somewhat epitomized, presentation of both general and special pathology. A main factor in the success of the book has been its lucid style and an unfailingly firm grasp of principles as well as of details. Herein T. Mitchell Prudden's influence still persists. The successive editions have reflected faithfully the progress in the meantime, and American contributions have received welcome attention. Of the advances in the four years since the previous edition, Dr. Wood, who has carefully revised the last five editions, dwells particularly on the new knowledge concerning various hormones and vitamins. The revision appears to be adequate, and new references, chiefly to monographs, have been added.

Physiopathologie de la thyroïde. Diagnostic et traitement des goitres. By Lucien Dautrebande de la Fondation Reine-Elisabeth; Membre correspondant de l'Académie Royale de Médicine de Belgique. (Avec la collaboration du Dr. A. Lemort.) Price, 40 francs. Pp. 326, with 36 illustrations and 40 tables. Paris: Masson & Cie, 1931.

The material in this book is handled in eleven chapters as follows: 1, physiopathology of the thyroid gland; 2, hypothyroidism; 3, endemic goiter; 4, simple goiter; 5 nontoxic adenoma; 6, toxic adenoma; 7, hyperthyroidism without the

usual symptoms; 8, hyperthyroid rheumatism; 9, degenerative changes in adenomas of the thyroid; 10, exophthalmic goiter; 11, treatment for hyperthyroidism.

The book is a summary of the various therapeutic measures employed in the treatment for thyroid disorders, critically reviewed by the open-minded Belgian author.

Pathologic physiology and biochemistry are discussed at length in a lucid and interesting style. Owing to the fact that similar or even identical gross pathologic and histologic changes are seen in the different clinical varieties of diseases of the thyroid, the classification is based mainly on the analysis of clinical findings and on the determination of the basal metabolism; the latter is considered the only absolutely reliable means of diagnosing thyroid disease. The author emphasizes the conception that various types of hyperthyroidism are not so strictly separated as is commonly believed and that there are frequent transitions and borderline cases. Many of the tables and all of the fifty-nine detailed case reports illustrate the effects of the different therapeutic methods. The author champions his method of using small but frequent doses of iodine (for instance: 2 drops, from ten to fifteen times daily). Many so-called iodine-resistant cases responded to this form of medication.

Though the book is primarily intended for the clinician, the pathologist will read with interest the theoretical chapters and will find the thirty-five pages of the bibliography particularly useful.

Books Received

APPROVED LABORATORY TECHNIC: CLINICAL, PATHOLOGICAL, BACTERIOLOGICAL, SEROLOGICAL, BIOCHEMICAL, HISTOLOGICAL. Prepared under the Auspices of The American Society of Clinical Pathologists by John A. Kolmer, M.D., D.P.H., D.Sc., LL.D., Professor of Pathology and Bacteriology, Graduate School of Medicine, University of Pennsylvania; Professor of Immunology and Chemotherapy, School of Medicine, Temple University; Head of the Department of Pathology and Bacteriology, Research Institute of Cutaneous Medicine, and Fred Boerner, V.M.D., Associate Professor of Bacteriology, Graduate School of Medicine, University of Pennsylvania, assisted by C. Zent Garber, A.B., M.D., and Committees of the American Society of Clinical Pathologists. Price, $7.50. With 11 colored plates and 300 illustrations in the text. New York: D. Appleton and Company, 1931.

LEHRBUCH DER SPEZIELLEN PATHOLOGISCHEN ANATOMIE FÜR STUDIERENDE UND AERZTE. Von Dr. Eduard Kaufmann, o. Professor der allgemeinen Pathologie und pathologischen Anatomie an der Universität Göttingen, Geheimer Medizinalrat. Neunte und zehnte, völlig neubearbeitete und stark vermehrte Auflage. Zwei Bände. Erster Band. Price, 55 marks. Pp. 990. Mit 506 Abbildungen im Text und auf färbigen Tafeln, zuallermeist nach Originalzeichnungen des Verfassers. Berlin: W. de Gruyter & Co., 1931.

DIAGNOSIS IN JOINT DISEASE: A CLINICAL AND PATHOLOGICAL STUDY OF ARTHRITIS. By Nathaniel Allison, M.D., F.A.C.S., Professor of Surgery, in Charge of Division of Orthopedic Surgery, University of Chicago, and Ralph K. Ghormley, M.D., Associate in Orthopedic Surgery, Mayo Clinic. From the Orthopedic Service of the Massachusetts General Hospital and the Harvard Medical School (1924-1930). Assisted by the DeLemar Mobile Research Fund. Cloth. Price, $9. Pp. 196, with 71 illustrations. New York: William Wood & Company, 1931.

FURTHER INVESTIGATIONS ON THE VARIOLA-VACCINIA FLOCCULATION REACTION. By James Craigie and W. J. Tulloch, Medical Research Council, Special Report Series, No. 156. Pp. 129. London: His Majesty's Stationery Office, 1931.

MEDICAL DEPARTMENT, UNITED FRUIT COMPANY. NINETEENTH ANNUAL REPORT. Pp. 276. 1930.

NUTRITIONAL ANAEMIA IN INFANCY WITH SPECIAL REFERENCE TO IRON DEFICIENCY. By Helen M. M. Mackay assisted by Lorel Goodfellow. With a Statistical Appendix by A. Bradford Hill. Medical Research Council, Special Report Series, No. 157. Pp. 125. Price, 2 shillings 5 pence, net. London: His Majesty's Stationery Office, 1931.

A TEXT-BOOK OF PATHOLOGY. By Francis Delafield, M.D., LL.D., and T. Mitchell Prudden, M.D., LL.D. Fifteenth edition revised by Francis Carter Wood, M.D., Director of the Pathological Department, St. Luke's Hospital, New York. Fabrikoid. Price, $10. Pp. 1339, with 850 illustrations. New York: William Wood & Company, 1931.

ASTHMA AND HAY FEVER IN THEORY AND PRACTICE: Part 1. Hypersensitiveness, Anaphylaxis, Allergy. By Arthur F. Coca, M.D., Professor of Immunology, Cornell University Medical College; Part 2. Asthma. By Matthew Walzer, M.D., Instructor in Applied Immunology, Cornell University Medical College; Part 3. Hay Fever. By August A. Thommen, M.D., Lecturer in Medicine, University and Bellevue Hospital Medical College. Cloth. Price, $8.50. Pp. 851, with 102 illustrations. Springfield, Ill.: Charles C. Thomas, 1931.